DECEMBER, 1952

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BRAIN

VOL. 75, PART 4.

THE SIGNIFICANCE OF PERCEPTUAL RIVALRY RESULTING FROM PARIETAL LESION[1]

BY

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OF the various disorders in sensation resulting from damage to the parietal lobe of the brain, that which concerns the lack of appreciation of a stimulus on the affected side of the body when an equivalent stimulus is simultaneously presented on the unaffected side of the body is especially remarkable. Bender and his associates, in a series of papers (Bender, 1945, 1946; Bender and Furlow, 1945; Wortis, Bender and Teuber, 1948; Bender, Shapiro and Schappell, 1949; Bender, Fink and Green, 1951) have described the phenomenon in examples of both localized and of generalized lesions of the brain. The absence of perception of a stimulus on the affected side was termed sensory "extinction." Others have referred to it as sensory "suppression" (Furmanski, 1950), postulating an active inhibition of the abnormal sensation by the normal. Critchley (1949) has recently reviewed the question, including early references to the phenomenon by Oppenheim (1885), Maas (1910) and Pinéas (1931), and returned to the conception of a defect in attention postulated by these earlier writers. Though the subject has been so recently discussed in detail in the excellent article by Critchley, we may attempt to summarize the more pertinent facts regarding the phenomenon. Bender (1945, 1946) and Bender and Furlow (1945) have clearly demonstrated that the defect is not solely related to tactile or painful stimulation, and that the double stimulation need not be symmetrical or of like kind. Critchley (1949) states that even vibratory sensibility, usually considered not to be affected by cortical lesions, may be suppressed by simultaneous stimulation of the opposite side. Partial degrees of the phenomenon, such as rise in threshold, lengthening of adaptation time, or dulling of pain, may occur instead of complete extinction, and the phenomenon may be overcome by strengthening the stimulus on the affected side, so that both stimuli are then perceived. The interaction of the stimuli in time is such that a brief stimulus on the affected side is not perceived if

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it follows that on the normal side within a period which is stated to be approximately three seconds (Critchley, 1949). Thereafter it is perceived as a separate event. On the other hand, a continued stimulus on the affected side may not be perceived for as long as half a minute after discontinuing a painful stimulus on the sound side (Critchley, 1949).

If one member of a pair of rival stimuli can be thus demonstrated to overcome the other, it is natural to seek for some evidence of defect in the stimulus which has thus been extinguished or dominated by another. Oppenheim maintained that "tactile inattention" as demonstrated by double stimulation may be the only demonstrable defect in sensation. Critchley has discussed this question in relation to later observations and concludes that "inequality in intensity of the percept may possibly be an essential condition though there are not yet enough data to be dogmatic on this point." When the phenomenon is most obvious various degrees of associated sensory change have been noted. Severe "cortical type" of sensory loss is not necessarily present, but when the disturbance was severe, imperception of one side of the body, allocheiria and visual inattention in the corresponding half-field, have been commonly noted. Since disturbance of discrimination of two points on the affected side of the body has long been known to be a prominent disorder from lesions of the parietal lobe, it is of great interest that Critchley concludes that tactile inattention is "quite independent of the phenomenon of defective tactile discrimination as demonstrated by the compass test" (p. 546), on the grounds that the single sensation from the compass test is referred midway between the two points, and that ipsilateral inattention is more severe in the peripheral parts of the limbs. We are not convinced of the validity of these objections. Reference to the careful observations of Head on two-point discrimination (Head, 1918 and 1920, p. 697) appears to us to confirm the relation of "extinction" to loss of such discrimination, provided that tactile sensation, by Head's criteria, was not altered. Wortis, Bender and Teuber's (1948) explanation of the phenomenon was that "perceptual responses, even to a discrete stimulus, depend on the total distribution of stimuli over the entire field at the time of stimulation," requiring consideration of total patterns of excitation. Abnormal gradients in excitability in the nervous system were thought to be necessary for its explanation, but the phenomenon was considered "refractory to any simple physiologic explanation." Though Bender maintains that the direction of the attention of the patient to the affected part will not abolish the phenomenon, Critchley states that this is not always so, and that since expectancy is so difficult to eliminate or control, he prefers to explain that phenomenon as a defect in attention. Russell (1951) comments on an associated phenomenon in the affected visual field so that small stationary objects tend to disappear, but reappear if the object is moved or if the subject blinks. This appears to us to be another aspect of the rapid adaptation which Bender (1945) found

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allied to extinction. Russell found persistent extinction phenomena only following severe and deep lesions of the parietal lobe, and suggested that the defect was due to delay in relaying sensory stimuli to the sound hemisphere when they were blocked by earlier arrival of the natural stimulus for that hemisphere.

The work of Head and Holmes (1911) and Head (1918, 1920) on defects in sensation resulting from cortical lesions is still the basis of clinical tests in use today. Though these authors were not concerned with the phenomenon of extinction of a double stimulus it is remarkable that they also concluded that a defect in attention localized to the affected part of the body was an essential feature of the cortical disturbance. Following a series of studies of defects in various kinds of sensation resulting from lesions of the spinal cord brain-stem and thalamus, they concluded that the defect from cortical lesion stood apart from all these in three respects, "first of all, the answers given by the patient are inconstant; at one moment he seems to appreciate a stimulus of a certain intensity, at the next it remains entirely without effect in his consciousness" (Head, 1920, p. 668). Increase in strength of stimulus was not necessarily more effective. There was no threshold for effective stimuli. "... we are no longer confronted with a gross physiological defect, but with what appears to be a want of attention." "We are above the level at which the defects in sensibility are due to interference with afferent impulses and the disturbances produced by a cortical lesion are manifested in defective attention and discrimination" (p. 669). Such changes were considered "essentially psychical." "Secondly, a cortical lesion tends to destroy the power of appreciating the difference between two objects which have certain basic sensory qualities in common," leading to defects in estimating weight, size and form, roughness or smoothness. "Thirdly, the cortex is responsible for the spatial aspects of sensation," leading to defects in recognition of posture, compass points, and tactile localization. "But these changes in sensibility are curiously uncertain. A varying reaction to constant stimuli, hallucinations and wrong answers of all kinds mar the measured records to an extent not usually present when the lesion lies at lower levels of the nervous system." Head and Holmes (1911) well recognized that at a conscious level a sensation did not stand as an isolated event, and that all comparative aspects of sensation, particularly a perception of posture but also of localization, required some comparative appreciation of all other sensations in order to have significance. "For this combined standard, against which all subsequent changes in posture are estimated, before they enter consciousness, we have proposed the word 'schema'." "A cortical lesion tends to destroy such schemata and so disturbs the certainty of spatial recognition" (Head, 1920, p. 669).

This brief summary of the extensive and fundamental studies of Head and Holmes should be sufficient to indicate that the phenomenon

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variously called tactile inattention, sensory extinction or tactile suppression, has attributes which belong to the whole class of cortical disorders of sensation, exhibiting all three of the peculiarities of such disorders defined by Head and Holmes. There does not appear to have been any attempt to define these relationships. We have recently had under continued observation a patient who not only presented an extreme degree of sensory extinction and associated imperception of one side of the body, but in whom these phenomena presented aspects which appear to us to indicate a fundamental defect in perception, common to them all and capable of interpretation in terms of uniform physiological function of the parietal lobe.

Case Presentation

M. C., a 55-year-old widow, was admitted to the Neurological Service of Boston City Hospital in January 1951. She complained that her left arm had "felt dead" for the past four days. On the day of onset of her difficulty while doing housework she suddenly noticed that her left arm felt numb and unnatural. At this time, when she walked she staggered a little, tending to veer to the left. She was still able to walk and denied all other symptoms. The next day, Sunday, she stayed home from church, a thing she very rarely did, and her friends noticed that she had lost her usual concern over her household affairs. The patient denied any progression of her symptoms.

When first admitted to hospital, the patient showed a slight left hemiparesis, and a left inferior quandrantic homonymous field defect to confrontation test, but these were no longer present after the second day in hospital.

Her past history revealed little relevant data. She had suffered from tuberculous adenitis of the neck at the age of 10, but after draining this healed spontaneously. The cause of her parents' death is not known. She had not suffered from venereal disease and claimed excellent health all her life.

Examination showed her blood pressure to be 170 mm. of mercury systolic and 95 mm. diastolic. There was no fever and her pulse was regular. She appeared to be a well-preserved woman of middle age, sitting comfortably in bed and smiling rather fatuously. The left hand was held with the fingers extended a few inches above the bed covers and remained in this position during most of the examination. The manner in which she had arranged her hair was striking, the right side of her hair being neatly put up in braids, while the left of her hair hung in disarray.

The neck was pitted with healed scars from cervical adenitis in childhood and there was a small, firm thyroid nodule palpable on the right side. Both carotids pulsated well. The lungs were not abnormal and the heart was not enlarged. The heart sounds were regular at 96 per minute and there were soft grade II systolic murmurs over both apex and base. The rest of the general examination revealed no unusual findings.

Neurological examination showed that she was fully oriented to time, place and person. She had no comprehension of the nature of her disability nor any concern about it. She smiled continually, and frequently said that there was nothing wrong with her and she would be all right once she got home. She was able to repeat 8 digits forward and 5 backward. Memory for past and recent events was intact, and knowledge of contemporary events such as the President of the United States, the Mayor of Boston, and the progress of the war was remarkably complete. She could solve simple mathematical problems, and serial subtraction of 7 from 100 was correctly performed. Judgment, however, was impaired. She was unable to make suitable plans for the future or to comprehend her disability even after it had

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been explained to her. She expressed little concern over her young daughter who had failed to visit her for several days.

The sense of smell was normal. The optic fundi were of natural appearance except for some narrowing of the arterioles. Testing the fields by confrontation and with the Bjerrum screen and perimeter showed no defect. On bilateral confrontation it was apparent that there was a left attention hemianopia. The pupils were regular, equal in size and reacted promptly to light and in accommodation. The extra-ocular movements were normal, but the corneal reflex was diminished on the left. Light touch and pin-prick were felt, but poorly localized, over the left side of the face. Bilateral stimulation was felt as a single sensation on the right. The other cranial nerves were normal and taste was preserved on both sides of the tongue.

No motor weakness could be demonstrated. The left hand was held and used naturally, but during examination it assumed an unnatural posture with the wrist and fingers extended. Rapid rhythmical movements were performed a little more slowly with the left hand than with the right. When using her right hand in cleaning her teeth or writing, the left hand remained in a stiff posture, pronated with the fingers extended. If the examiner approached her left hand to grasp it, the hand would move involuntarily as if to avoid the examiner's hand. When the examiner grasped the left hand and passively flexed or extended the wrist or elbow a resistance to such passive movements was felt. This resistance had a purposeful character, as if opposing an anticipated movement. The hand frequently grasped the examiner's coat or the arm of the chair very forcibly. At other times no rigidity, spasticity or abnormal posture was demonstrable in the upper or lower limbs. The active movements of the patient were carried out rapidly and freely. The left hand was used quite naturally in any movement requiring the use of both hands, e.g. tying a knot, or buttoning a garment. There was no defect in motor power. Neither grasp nor sucking reflex was present. Her gait was not abnormal but if her left slipper fell off she would continue walking, leaving it neglected where it lay. The biceps, triceps, radial, finger, patellar and Achilles tendon reflexes were all slightly more active on the left side. The only abdominal reflex obtained was in the right upper quadrant. The left plantar response was extensor, the right flexor. Appreciation of very light touch with cotton was not felt in the left arm but was intact in the left leg. Pressure of the finger was felt in the left arm. Light touch and pain were correctly felt on the right side of the body. A single pain stimulus was felt but poorly localized on the left side of the body. Vibration sense was intact and felt the same wherever tested. Position sense was intact on the right, but poor in the left fingers and toes. Her answers in testing coarse passive movement in these joints were wrong on the average of four times out of ten. Frequently she would say, "I do not know," or "Did you move it?" but she would not admit to guessing. Position sense was correct in the proximal joints on the left such as the shoulder, elbow and knee. Temperature sensation to brief contact with the bottom of a test tube over the left side of the body was not felt, but if the surface area tested was large enough, then the stimulus was appreciated.

Stereognostic sense and ability to recognize skin-writing were lost on the left side. Tactile localization and two-point discrimination were consistently inaccurate over the left side of the body. Tactile inattention was easily elicited with two simultaneous stimuli. We shall describe these disorders in greater detail below.

Laboratory studies showed normal urine without glucose, albumen, or unusual sediment. The hæmoglobin was 13·5 grammes per cent, and the white blood count was never elevated. The blood Hinton was negative, and the blood urea nitrogen 15 mg. per cent. Lumbar puncture at the time of admission showed clear colourless fluid with an initial pressure of 130 cm., 1 lymphocyte and 1 red blood cell per c.mm., protein of 25 mg. per 100 c.c., and a negative Hinton test. Chlorides, sugar and colloidal gold tests revealed no abnormality.

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Electroencephalograms were done on February 12 and February 26, 1951, both records showing the same abnormality. Dr. C. W. Watson reported that there was paroxysmal circa 30 per second activity of excessive relative amplitude throughout the tracing except for the right central, temporal, parietal, and occipital regions. In the latter areas there was poorly modulated, high relative amplitude slow activity.

A Wechsler-Bellevue intelligence scale was attempted and the patient scored a verbal I.Q. of 41. However, she was completely unable to carry out the performance tests. She could not put together the simplest of the block designs. She was unable to comprehend any of the pictures, for example an unfinished house she called a fence. Detailed analysis of her defect is described below.

Arteriography was discussed with the patient and her family but was not performed at their request. Roentgenograms of the chest and skull revealed no abnormality.

The patient remained under observation in hospital for two and a half months and although there was some improvement in the first two weeks, her course thereafter was stationary. She was re-examined after leaving the hospital, the last occasion being eleven months after her illness began. No improvement of the disorder had occurred in eleven months, except that after giving careful thought to the problem the patient could now put on a coat without error.

The clinical diagnosis was infarction of the right parietal lobe, due to thrombosis of ascending parietal branches of the right middle cerebral artery.

Special Disorders

Apraxia of dressing.—The patient had great difficulty in dressing herself and needed frequent nursing assistance. Her difficulty was of a special kind; she could dress the right side of her body but neglected the left side. When handed her bath robe, she attempted first to put her right hand into the left sleeve. Next she pulled the rest of the robe around her left shoulder and was totally unable to put her left arm through the proper sleeve. She then lost the sleeve and appeared satisfied that the process was correctly complete (fig. 1). When helped into her robe, she was unable to tie it since she could not pass the left end of the belt to the right. Finally when presented with both ends correctly placed she could only make the right hand loop of a bow (fig. 1, *c*) and the ends fell apart untied. She appeared mystified by the falling of the right end on release, caught it again, and tried to put it into place. The left end was thereafter entirely neglected (fig. 1, *d*). When being examined the patient modestly adjusted her clothing on the right while parts of the left side of the body were heedlessly exposed.

Orientation in space.—She had no difficulty in finding her way around the ward, and never approached the wrong bed, even if taken by a devious route into the ward kitchen and allowed to return to her room. She was able to recall her way even if both left and right turns had to be negotiated. She was able to hold a stick horizontally or vertically on command with her eyes open or closed, and was able accurately to grasp objects held in the left visual field, with either hand.

Two months after discharge from the hospital she was asked to recall as much about the ward as she could. She began by describing all

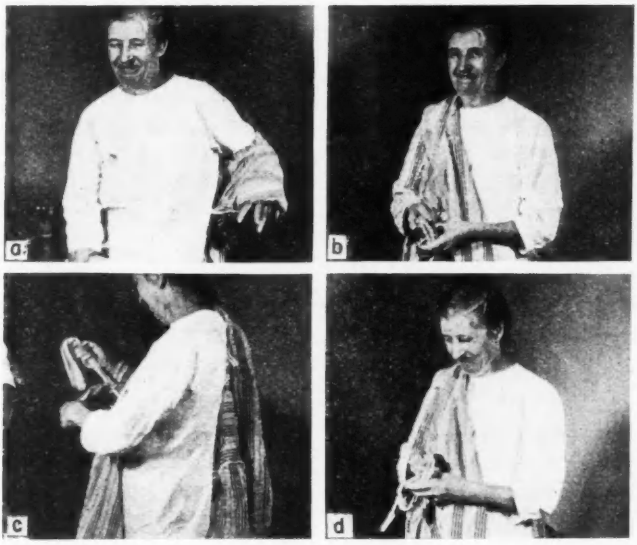

FIG. 1.—From a moving picture of M. C. *a* shows the patient just after she had been requested to remove her dressing gown. The left sleeve is not removed, though she is under the impression that she had taken it off completely. Note the abnormal attitude of the left hand which later comfortably grasped the arm of the chair. *b* shows the patient after she had been asked to put the dressing gown on. She is unaware that the left arm failed to enter the left sleeve. *c* and *d* she was asked to tie the belt of the garment, and has formed a loop at one end which she is tying to the end itself, unaware that it does not encircle her waist.

the patients and the windows which had been on her right, mentioning them from right to left. She made no mention of the patients on the left until pressed and then was able to recall 2 out of 5. In a similar manner when asked if there were not more windows or a door on her left, she was able to describe them together with a washbowl and a television set that had been on her left. When asked about the corridor from the ward she mentioned the rooms and the nurse's desk on her right but only mentioned the staircase and the rooms on the left when asked "what did you pass on your left?" She was able to find her way round her own apartment, could indicate correctly where various rooms were without looking, and could indicate their layout correctly on a rough diagram.

Writing.—Her ability to write was strikingly well preserved. She was able to take dictation or write composition legibly but she only utilized the right-hand side of the paper. The writing became successively more cramped to the right margin. The words were correctly spelled and the letters well formed except that the "t's" remained uncrossed; the "i's"

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undotted. She could write numerals correctly and write a simple addition. Copying was limited by her reading difficulty, and reproduced the same defect.

Reading.—She was able to read newspaper headlines slowly, frequently spelling the words out with her finger, and could carry out short written commands. She was unable to read more than three or four lines of small type because she failed to read the first few words on the left side of each new line, and frequently transferred to the wrong line. The words were correctly read.

Speech.—There was no motor or sensory aphasia. Her spontaneous speech flowed easily and readily. She named simple objects correctly and understood and carried out verbal commands of moderate complexity. She was able to visualize objects and give a reasonably good description of them, including their colour.

Apraxia.—Although she was able to feed herself, clean her teeth, use scissors and carry out other complex motor activities, she had a particular type of difficulty in copying designs. She was unable to reproduce accurately any design involving more than three blocks or matchsticks; it was striking that the errors were predominantly on the left side of the design (fig. 3, *g*). She showed a marked tendency to "close in" on the model to be copied, bringing her own blocks or matchsticks as close as possible to the test model. In copying designs she cocked her head sideways and the defective portion of her design reflected the posture of her head, being most marked in that portion corresponding to her left visual field. Even when the defect in her model was pointed out to her by the examiner, she was still unable to correct it.

Abnormal postures.—There was no abnormality in posture in the left limbs or body, except during examination. It was observed that when she was being questioned or examined there was a tendency for the patient to extend the fingers and wrist of the left hand, and to maintain this attitude until her attention was directed to it, when it immediately relaxed and assumed a natural posture. The phenomenon was more obvious if the arms were outstretched (fig. 2, *a*) and the left limb then tended to rise higher. Even if the eyes were open this deviation became very gross if the attention of the patient was diverted elsewhere (fig. 2, *b*). If the left arm had been resting naturally on the bed, or the arm of a chair it slowly raised as the examiner approached (fig. 2, *c*), particularly if the approach was from the left side, or if one examiner stood on each side. When the attention of the patient was directed to the phenomenon the limb was relaxed, with some embarrassment, but "levitation" again occurred when the attention of the patient was redirected elsewhere. In testing visual fields with coarse stimuli, recognition of movement in the left field was accompanied by more rapid spontaneous raising of the

FIG. 2.—To show the abnormal postures of the left hand. *a* outstretched with the eyes closed. *b* further deviation, which occurred with the eyes open or closed. *c* spontaneous levitation of the left hand which occurred during examination. *d* spontaneous levitation of the left hand and a movement towards the examiner's fingers when asked if she had seen anything move (the examiner's fingers had just moved rapidly).

left hand toward the stimulus, turning the palm towards it (fig. 2, *d*), though no such movement occurred on the right side, and the patient had been asked not to move.

If the examiner passively imposed a posture on the left limb, the original resting posture was quietly resumed. There was no catatonia, or catatonic persistence of attitudes.

Drawing.—The patient could draw a recognizable square, or a circle, from memory. With more difficult objects such as a face or a house, she was unable to complete a recognizable whole (fig. 3, *a*, *b* and *c*). The patient had great difficulty copying a drawing, for example the left side of a square was left out, a pattern was reproduced in separate parts and in copying drawings such as a house or a train, the right side was correctly drawn in detail but the left side totally ignored (fig. 3, *e*, *f*).

Calculation.—Serial subtraction of seven from one hundred was well done, and simple arithmetical problems were correctly solved. Numbers could be perceived and written accurately.

Interpretation of proverbs.—The patient gave only elementary and categorical interpretations of many well-known proverbs.

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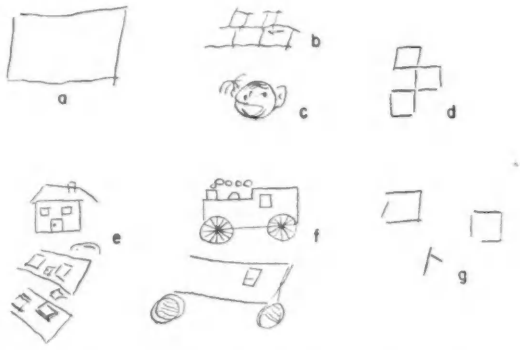

FIG. 3.—*a* a square drawn by the patient, without example. *b* a house drawn from memory. *c* a drawing of the face from memory (note the several ineffectual attempts at a right ear, and that the eyes, nose and mouth are represented, though poorly so). *d* a pattern formed by matchsticks, of which the copy by the patient is shown in *g*. *e* drawing of a house made by the examiner, and below it two attempts of the patient to copy it. *f* example of an engine drawn by the examiner, and below it the attempt of the patient to copy it.

Identification of body parts.—The patient could correctly identify fingers and thumb and other parts on either left or right side on her own body and on the examiner. She could identify a left and right shoe or glove, and put them on the appropriate foot or hand. The left shoe was put on with the tongue turned in, and in putting on the left glove, she had great difficulty preventing two fingers from getting into one glove finger. When presented with a mannikin and stimulated on a part of her own body, she was able to identify on the mannikin the appropriate part. However, of ten trials she confused sides on four occasions. On each of these occasions she pointed to the right side of the mannikin when her left arm or leg had been stimulated.

Bimanual dexterity.—Complex co-ordinated movements of both hands showed no defect of motor performance. She was able to put on her shoes, comb her hair and wash her hands. She combed the left side of her hair if instructed to do so. In carrying out complex movement requiring both hands, such as in tying a knot, she oriented herself so that her hands were working in her right visual field.

Though she could successfully fold a piece of paper and put it in the envelope there was a special difficulty connected with folding the paper. She approximated two corners, held the corners with the left hand, and then attempted to crease the fold in the paper. At this step the grip on the corners was released and the crease proved asymmetrical. A renewed attempt was then made with the same result. Eventually an approximate folding in half was achieved, but the same difficulty recurred in making a second fold.

Tactile discrimination.—Loss of tactile stereognosis in the left hand was complete. The patient was totally unable to recognize size, shape and form of objects palpated by the left hand with the eyes closed, even if they were as large as a chair. A square piece of soap felt by the left hand was described as "A round piece of iron, not very smooth, it has sharp edges, but I would not know the size." As soon as she felt the soap with the right hand, the answer was correctly given. A flashlight battery was described as "round, hard, not like butter, not made of cloth or paper." A rubber ball she said was "not a knife, not sharp, it is hard, has no give, not rubber, I think it is round, I do not know the size, it feels like cork." She was unable to identify a shoe, or hat or brush, though there was no difficulty in recognizing such objects with the right hand. There were as many errors in appreciating the presence or absence of very light touch with one as with six hairs on the left upper limb. A heavier contact with a few hairs did not increase the frequency of correct response, but contact with a piece of cotton 5 sq. cm. in area was immediately accurately perceived, and in comparison with equal pressure from a few hairs was said to be "easier to feel."

Texture of fabric.—A folded cotton sheet felt with the left hand was described as "the same material as your coat." She said she did not know what a towel and a piece of gauze were, but readily recognized them with the right hand.

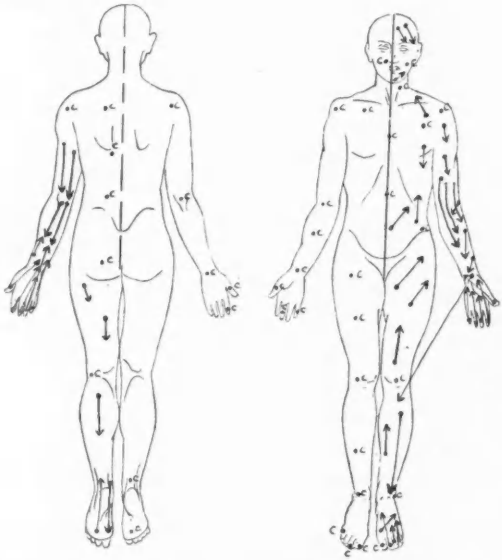

FIG. 4.—Tactile localization. Touches correctly localized are shown marked with *c*. Incorrect localization, and the direction and approximate extent of reference are shown by line and arrow.

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Tactile localization.—Consistent errors were made in localizing a stimulus in any part of the left side of the body. The deviations varied from a few inches to a complete limb segment (*see* chart, fig. 4). Rarely, a stimulus in the left hand was localized on the left leg (*see* chart). The greatest loss was in the left arm, the least defect over the face.

Position sense.—When the patient's forefinger was placed through a hole in a horizontal board, passive movement of the finger was perceived, but sense of direction of movement, and of posture, was lost on the left side, e.g. she would answer "downward" or "to the left" correctly on the right side but could only answer "You moved my finger" on the left. This was further demonstrated by passively placing her finger on a board, marking the spot, moving her finger and asking her to replace the finger in the same place. This could be performed correctly on the right side but not on the left. Position sense was intact in left knee, ankle, shoulder and elbow.

Tickling and scratching.—Tickling and scratching of either side of the body was felt equally on the two sides. When carried out simultaneously on the two sides these were felt only on the right side.

Summation of pain.—Repetitive pin-pricks when carried out independently on each side were found to be equally unpleasant and she did not report any burning quality or altered sensation.

Dysæsthesias.—She never complained of spontaneous pains, nor did music or pleasant stimuli in general produce any different sensation from the left side. Deep pressure evoked no more of a painful response on the left than it did on the right.

Weights.—Weights from a chemical balance were tested in either hand independently. In this manner she was able to recognize differences in weight as small as 30 grammes in either hand, providing the weights were not placed in both hands simultaneously. When weights were compared in the left hand only she was able to name the heaviest weight correctly when 5, 10 and 20 gramme weights were held one after the other. However, when 100 grammes were placed in both hands simultaneously, it was felt only on the right, the left weight was totally ignored and it balanced in her hand precariously or was allowed to fall.

Temperature sensation.—With two test objects (test tubes), each stimulating a surface area of 1/2 sq. in. and having a temperature of 7 and 61° C. respectively, the patient was able to distinguish hot from cold on the right side without error. When any part of the left arm and leg or trunk were stimulated she stated she felt no difference between hot and cold. Over the left face she made three errors with ten trials. When a needle was heated and applied to the left hand so as to redden the skin she could not state whether it was hot or cold and made no movement

to brush away the noxious stimulus as she did when the right hand was stimulated.

By using measured degrees of temperature and larger areas of contact it was evident that the sensory defect was greatest in the left arm and less marked over the left face than the left leg, and that increase of surface area greatly increased the proportion of accurate responses. Control tests on the right were consistently correct. Table I gives the consecutive responses in one such trial, and shows the large number of equivocal responses which characterize this type of test.

TABLE I

Surface area of stimulus in square inches	*Temperature in ° C.*	*Area stimulated on left side*	*Reply*
A. Eyes closed			
2 sq. in	11°	Forearm	"Hot"
2 sq. in.	42°	Forearm	"Not very hot"
2 sq. in.	40°	Forearm	"More warm than cold"
2 sq. in.	11°	Leg	"Cold, isn't it?"
2 sq. in.	42°	Leg	"Not as cold as before"
3 sq. in.	57°	Arm	"It isn't cold, I know that—hot"
3 sq. in.	7°	Arm	"Cold, isn't it?" (winces) "Hot"
3 sq. in.	4°	Arm	"I think cold"
3 sq. in.	57°	Leg	"It isn't very hot"
12 sq. in.	22°	Shoulder	"Hot"
20 sq. in.	70°	Shoulder	"Warm"
12 sq. in.	22°	Leg	"It does not feel warm"
20 sq. in.	70°	Leg	"It's hot"
20 sq. in.	70°	Shoulder	"It's more cold than hot"
12 sq. in.	22°	Leg	"It does not feel cold"
12 sq. in.	22°	Shoulder	"Hot"
B. Eyes open and looking ahead			
20 sq. in.	80°	Arm	"It feels hot!"
20 sq. in.	80°	Shoulder	"Hot!"
12 sq. in.	80°	Shoulder	"Hot, but hotter before"
20 sq. in.	80°	Shoulder	"Hot!"
12 sq. in.	80°	Shoulder	"Hotter before"
20 sq. in.	80°	Leg	"It's warm"
12 sq. in.	22°	Leg	"It's not as hot as before"
12 sq. in.	80°	Arm	"It isn't very hot"
6 sq. in.	80°	Arm	"It is not hot or cold"
20 sq. in.	80°	Leg	"Hot"
12 sq. in.	80°	Leg	"Not as hot as before"

Each entire side of the patient's body was independently exposed to a radiant heat lamp at different distances up to 8 feet. When tested in this manner, she reported a feeling of warmth with equal rapidity on either side.

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Visual recognition.—When looking straight ahead, without fixing on any particular object, the patient could immediately identify large objects such as a hat, shoe, can opener, scissors, exposed for less than half a second in any part of the periphery of the left visual field. Small objects such as part of a key, 3 cm. long, required to be introduced to a more central part of the left field.

With the tachistoscope the patient was seated 1 m. from a screen and a single projected number or letter 6 in. in size was recognized in all four quadrants of the visual fields with duration of stimulus as short as 1/100 of a second. When the patient was shown the composite picture from Poppelreuter (1917) (fig. 5), she named everything correctly on the

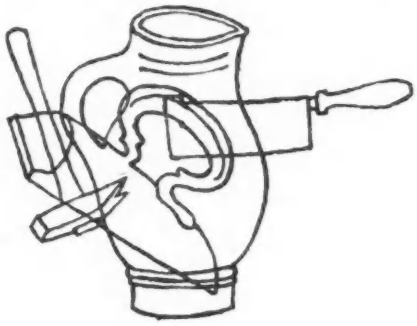

FIG. 5.—Composite diagram from Poppelreuter (1917). The patient named the pitcher and cleaver (Chopper). When the picture was inverted and shown to her again she named the hammer and the iron, but was unable to recognize any other object.

right side of the picture, e.g. the pitcher and the cleaver, but failed to notice the flat-iron and hammer which are on the left side of the picture. But when the picture was inverted she was able to recognize the flat-iron and the hammer but not the pitcher and cleaver, even when outlined by the examiner's finger. When two copies of the diagram were approximated to within 2 in. she correctly named all the objects represented. A composite diagram of common fruits and vegetables, each barely separated from the others, resulted in correct naming of those on the right side, followed by slower, but often correct, naming of those on the left side (a cabbage was called a flower). Inversion of the picture resulted in mistakes in those on the left side, previously identified (corn now called a banana). A composite picture of objects more widely separated from each other (kitchen utensils) resulted in rapid identification of all but one in the lowest left-hand corner and one in the middle. Performance therefore improved with separation of the elements of the diagram. The nature of this defect was further demonstrated by con-

fronting her with different objects, such as a large key, matchbox and scissors, separately in each visual quadrant. She was able in less than one second to name each one correctly. However, when two objects were presented simultaneously in both visual fields she was unable to identify the object in the left field but recognized the object on the right, even when the left object was large and moving, e.g. the examiner's hand.

In the dark room, using two light sources of equal intensity and 5 mm. aperture at 3 ft. the patient reported that two light sources in the left visual field were one, noticing only the upper of the two; although she was able to recognize the two lights in the right visual field. The inability to recognize two points of light in the left visual field had no relation to the degree of separation. This defect could also be demonstrated by confronting the patient with two fingers in the left visual field, but she was able to recognize two moving hands. It was also found that in the left lower quadrant of the homonymous visual field her replies were more frequently inaccurate. The duration of the stimulus played some part in that results were not consistent if the duration of exposure of stimulus was longer than one second.

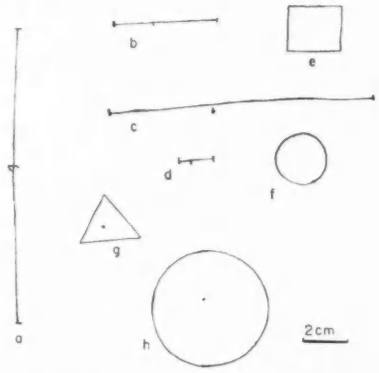

FIG. 6.—The patient was asked to mark the centre of a vertical line (*a*), and horizontal lines of various lengths (*b*, *c*, *d*), and of a rectangle, triangle and circles. The scale indicates the original size of the lines and figures, which were presented separately.

When asked to indicate the mid-point of a horizontal line, or the centre of a square, circle or other figure she invariably indicated a point well to the left of the actual centre (fig. 6). The proportion of a horizontal line to the left of her mark varied between 26 and 43 per cent. The mid-point of a vertical line was approximately correctly indicated (fig. 6, *a*). She could correctly show the longer or shorter of two lines, or the larger of two or more circles, however far apart they were, provided they did not intersect. In such judgments fixation was not maintained on any one point.

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Inattention deafness to direction of sound.—The patient had normal hearing acuity and was able to hear a single stimulus in either ear and correctly state the direction of sound. But with bilateral stimulation opposite each ear she said she heard the sound in both ears, but always reported erroneously that the direction of the sound was from the right.

Two-point discrimination.—By using the usual compass test with blunt points it was at once apparent that the patient was unable to recognize two simultaneous stimuli over the left hand or foot no matter how far apart the two points were separated. For example, with one stimulus applied to the left side of the face and one to the left foot she reported that she felt only one stimulus on the face (fig. 7). Similarly two stimuli

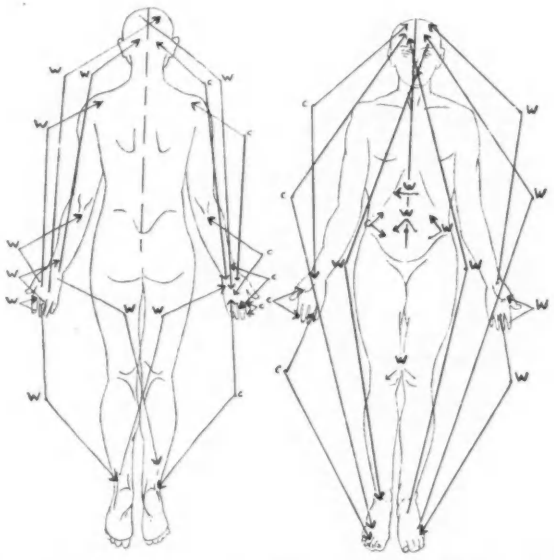

FIG. 7.—Two-point discrimination. The diagram shows a series of double blunt contacts, each pair being connected by lines, and the letter "c" where both contacts were reported, the letter "w" where only one contact was reported. The arrowhead represents the approximate site of the reported stimulus.

applied to the left hand and the left foot respectively were felt as one stimulus on the left leg. As soon as one stimulus was applied to the right side of the body and one to the left, as though a giant compass was being used, then she always reported feeling a single stimulus on the right. Two-point stimulation was always correctly reported on the right side of the body, but when one stimulus was applied to the right side of the body and the other to the left side within 2 in. of the mid-line (excluding the face) there was a variable response, the patient then frequently recognizing

the two stimuli. Of two stimuli applied together to any part of the left arm the more proximal was alone recognized (fig. 7), but its actual position was vaguely designated.

There was no difference in the type of response with pressure compass, and the response to two pin-pricks, or two touches with cotton. The one perception was neither less nor more localized. The extinction could readily be elicited with asymmetrically placed stimuli, and the stimuli did not have to be of equal intensity. Indeed, a very light touch with a pin on the right side of the body would inhibit a painful stimulus on the left. Furthermore, summation of stimuli, such as repeated pin-pricks on the left would not be felt by the patient if simultaneously the right side of the body was being subjected to a constant stimulus such as pressure or a firm pin-prick.

When two points were stimulated on the left side of the body the face was "dominant" over the arm and leg, and the leg over the arm. Similarly, the abdomen and shoulder were "dominant" over the arm, but when the hand and arm were simultaneously stimulated it was reported as a single stimulus in the hand and when the forearm and arm were stimulated she might feel this as a single stimulus in either forearm or arm or between the two points. In the leg the proximal part was "dominant" over the distal portion.

Asynchronous double stimulation.—When the right hand was stimulated with a single brief pin-prick, and the left hand with repeated pin-pricks, there was a period of 20 seconds before the repeated pin-pricks were felt in the left hand. Similarly, if the left leg was stimulated with a single pin-prick there was a delay of between 18 and 30 seconds before repeated pin-pricks were felt in the left hand. This latter test was made with a stop-watch on three different occasions with the following results. On the first attempt, after the single brief pin-prick on the left leg, repeated pricks on the left hand were not felt at all for 3 seconds, then she reported erroneously feeling a prick on the *left leg*, and after 18 seconds she correctly reported pain in the left hand. On the two other occasions after discontinuing the pin-prick over the left leg she felt nothing for 20 and 30 seconds respectively, when she recognized the pricking in the left hand. Even gross bilateral stimuli such as clapping her sharply on both shoulders would cause her to turn to the right and were only felt on that side.

Single pin-prick appreciation.—Although the patient could appreciate a single pin-prick on the left side of the body, it was more rapidly and accurately appreciated over the left leg than in the arm. Localization was of the same order of inaccuracy as for touch. For example, when stimulated sharply with a pin-prick in the left hand she said slowly, "That felt like a pin." When touched lightly with the pin on the left hand and asked "Was that a pin-prick?" she then rubbed the area touched and said, "I don't think so." When the left calf was either sharply pricked

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or lightly touched with the point of a pin her answers were instantly correct, but vaguely localized to the leg.

Stimulation with multiple pin-points.—When multiple pins were passed through a cork and such prongs used together as a stimulus, then she showed improved performance in the rapidity of her response, but had a poor degree of appreciation of their multiplicity.

For example, when triple prongs were lightly pressed on the left hand, she immediately said "You touched me right here with a pin" and pointed to the left hand. When pressed with the question "How many pins" she replied "Two." Comparing the sensation of six light pin-pricks with one on the same part of the left hand she reported that each "felt like a pin." With heavier intensity of prick she said six pins "hurt more," but regarded them as a single stimulus. Withdrawal was more marked with six pins than with one. When seven prongs were used, they felt like "several" on the right hand, but as "two or three" on the left hand, and several on the left side of the face. On other occasions more than six prongs were necessary to evoke recognition of multiplicity.

Double simultaneous stimulation with multiple prongs.—Using a single stimulus on the right and multiple prongs on the left simultaneously, it was found that if the multiplicity of the stimulus on the left was gradually increased, a point could gradually be reached where *both* stimuli, on either side, were appreciated. For example, when the right hand was stimulated with one pin and the left hand with seven she felt the stimulus only on the right. However, when ten prongs were used on the left, she said, "You pricked me with two pins, one on either side." Exactly similar results were obtained when both knees were stimulated in the same manner. By asking the patient to concentrate carefully, her performance was improved, e.g. seven prongs used on the left and one pin on the right were felt on both sides correctly. When five prongs were used on the left and one on the right, she pointed first to her right hand then for a second to the left and then said, "I felt it here" and pointed back to her right hand and said "one, maybe two." With four prongs on the left and one on the right, she reported only one prick on the right.

When the left face and left arm were simultaneously stimulated in a similar manner with a single pin on the face and multiple prongs on the arm, she reported only a pin-prick on the face, even if ten prongs were used on the arm.

When the left arm and left leg were simultaneously stimulated, three to four times the number of simultaneous pricks on the forearm or hand were necessary to overcome the extinction caused by a stimulus on leg or knee.

When the left leg and left face were both stimulated with single pin-pricks she replied, "You are sticking my face," unless the pricks were

very severe. The reply was then, "I feel it in the leg and face, but I feel it in the leg more."

Bilateral vibrating tuning forks.—The simultaneous bilateral application of two tuning forks to any two parts was reported as "buzzing" only on the right side.

Dissimilar tactile stimuli.—Various combinations of dissimilar stimuli were tried on the two sides. It was found that light touch, pressure, temperature, vibration, when applied to the right were usually effective in suppressing pain on the left side of the body. We were not consistently able to cause tactile extinction on the left side of the body by an intermittent sound in the right ear or a tuning fork held over the right ear but louder continuous sounds were not used.

Illusory responses.—The patient gave no evidence of hallucinations, or of confabulation. Sometimes erroneous identification of objects was in terms of some other object in the same room.

Discussion

The patient was suffering from a presumed vascular lesion in the right parietal region. There was no persistent hemiplegia, aphasia, or visual field defect. The only residual positive neurological signs were a slight change in tendon reflexes, a persistent extensor plantar response, and a persistent defect in awareness relating to the left side of the body and extra-personal space. The loss of position sense, two-point discrimination, stereognosis, and of tactile localization are the classical signs of a disorder in the parietal cortex. This is the specific type of loss of the discriminative aspects of sensation so well defined by Head and Holmes.

There was no evidence of generalized disorder of cerebral function. Memory, speech, orientation for person, place and time, appreciation of current events and simple arithmetic were all within the range of the educational level of the patient. Judgment, however, was impaired and the placid oversmiling personality could be attributed to defect in general awareness and insight. The delinquency of her adolescent daughter became of little importance. Normally a devout woman, she became neglectful of her religious observance. She was persistently unaware of the nature, extent or severity of her illness and was incapable of making realistic plans for the future.

When her awareness of herself and her surroundings was explored, it became apparent that there was a very specific defect related to the left side in every sphere of activity. The defect was such that a stimulus had to be unique and uncomplicated to be appreciated, whether its nature was tactile, visual, painful, thermal, or kinetic. Furthermore, for virtually all kinds of stimuli, especially tactile, thermal and vibratory the slighter gradations were either not perceived or subject to great variability.

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Any more complex derivation from the stimulus was not possible, notably localization of tactile stimulation, estimation of heat on small areas, derivation of shape or texture of things touched. The gross event could be perceived. Visual perception of objects was much less impaired, so that recognition of common objects was swift and accurate even in the periphery of any part of the left visual field. Only with very small objects, such as a small key, could perception be shown to be defective in the left field.

In this patient there was a depression of perceptive function for the left side without loss of the elementary senses of touch, pain or temperature. This aspect of the disorder was most clearly demonstrable in terms of temperature where increase of area stimulated on the left side could compensate for the apparent defect. Within the constellation of sensory disturbances the most complete and extensive defect was in relation to two-point discrimination on the left side of the body. The degree of its disturbance was such as to make it impossible for her to perceive any two simultaneous stimuli as two separate events on the left side. It was possible to demonstrate this disorder even in the left field of vision. The other complete defect demonstrated by the patient was a tactile astereognosis in the left hand. Since tactile recognition involves concurrent perception of several tactile factors, it appears that complete astereognosis represents the same kind of defect that is shown by the loss of two-point discrimination. Thus, the sensory disorder might be viewed as first a loss of finer discrimination of intensity of touch, pain, temperature, vibration, and second, a complete inability to synthesize more than a few properties of a sensory stimulus taking origin from the left side. The very striking change in the general behaviour of the patient, namely her failure to attend to the left side of herself or of space can also be viewed as a disturbance of synthesis of multiple sensory data. This was seen in her gross failure to adjust her dress and hair, to report events or react to the presence of objects on the left side and was apparent also in her reading difficulty, and in the disturbance of localization of sound. The visual disorder was relative in degree, for she could recognize a single object introduced into the left visual field as a test, though she would neglect it in her natural behaviour. If under some circumstances such recognition is possible the mechanism of recognition must be essentially intact, and the explanation of failure must be sought in some complicating factor which interferes with the neural events leading to recognition.

With these preliminary deductions in mind we may now examine the defect in greater detail. In general the left-sided defect is an imperception, by which is usually meant an inability to reach a conclusion regarding the origin of multiple sensory data, the primary data being intact. Intactness in this sense implies that if only one light touch in ten on a given spot is perceived, the mechanism of conduction of light touch sensation is

present. If the perception of light touch on any of several neighbouring spots is similarly defective, yet a touch on all the spots at once is regularly perceived, the defect must be at some place where the sensory data from each spot can interact so as to reinforce each other. Further, each such touch must produce some sensation in order to interact with the others. In this class of disorder we must therefore distinguish between sensory conduction and perception. If a touch with one hair is not perceived at all, but of six hairs perceived one time in ten, it can also be assumed that the very light touch with one hair set up normal sensory conduction, and perception was at fault. Our patient could perceive contact more clearly and more regularly with a broad piece of cotton than with a few hairs, and usually could not appreciate contact with less than three or four hairs. It may be objected that if no thermal sensation was possible when the object was sufficiently small, for example, the bottom of a test tube, then primary sensation was indeed lost. But it could readily be shown that stimulation of a larger area yielded an appropriate perception of warmth or coolness, whereas stimulation of any single small part of it was not recognized correctly. Stimulation of a broad region, no part of it responding to a very small stimulus, could result in perception of small differences in temperature. The wider the area stimulated, the more accurate was the possible perception. Pin-prick was more frequently perceived as a prick when more than one point was used, and most consistently with many points. Therefore, each small part must transmit accurate information, for which full perception required in addition a spatial summation. This type of defect was present in varying degree in regard to all types of primary sensation. Such a defect indicates disorder in the appreciation of quantity of sensation. In the disorders of sensation resulting from peripheral nerve lesion and central sensory tracts a defect in quantity of sensory conduction is demonstrable by the use of graded intensity of point stimulation, which demonstrates either a raised threshold, or complete absence of sensation whatever the intensity of stimulus. As Head and Holmes demonstrated, the type of defect found in parietal cortical lesion has no such consistent threshold, in terms of intensity. We find, however, that it has a threshold in terms of multiplicity of similar points, a defect in the spatial significance of sensation. A heavy pin-prick might be a *severe* pin-prick in terms of eliciting nociceptive withdrawal, but to the disordered perception it is also a *small* pin-prick, too small perhaps to be recognized.

The patient thus clearly demonstrated the defects commonly attributed to "inattention." The unsatisfactory nature of this term is immediately apparent in the result of the test by which the patient was shown a picture of several test objects jumbled together, and correctly named those on the right, but was unable to name those on the left, even when their outline was traced with the examiner's finger. She could name them if the picture was inverted, so that the object

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now came in the right field. Here it was clear, as in the inability to recognize the pattern of an object placed in the left hand, that no degree of reinforcement of attention could potentiate the cortical discrimination so as to give a correct reply. This may appear inconsistent with the ability of the patient to recognize objects in the left field of vision for less than one second, while her gaze was directed at the examiner. The phenomena are not comparable, however, for if she were requested to perceive some fresh stimulus in front of her, such recognition in the left field was no longer possible. The composite diagram test showed that the general percept, in this case the whole diagram, determined the point of fixation, and that with fixation of vision all visual perception to the left of the fixation point was reduced. Without fixation, attention could be drawn to any part of the left visual field, as revealed by the tachistoscope. In the case of vision, therefore, the resulting percept itself lost discrimination on the left side. This was also shown by the test of bisecting a horizontal line, or indicating the centre of a circle or square. The total percept is biased to the patient's right because judgment of space to the left is underestimated. This contrasts with the ability of the patient to point to the largest or smallest of a series of circles or lines that did not overlap. This was immediately and correctly performed, probably because the images were separate and the complications introduced by a single perception did not interfere. In the case of bisecting a line or circle correctly no reinforcement of attention could overcome the defect. Impairment of attention was thus secondary to the disorder of perception. Two kinds of failure of perception were present, first an *absolute* inability as seen in tactile astereognosis, and second a *relative* inability dependent upon the presence of a prior stimulus. Attention could not affect the first, and could affect the second only by enabling a prior stimulus to be ignored.

The defect in recognition, whether of the left side of objects seen, or a pattern to be copied, or of the nature of things placed in the left hand, whether complete or partial, was the same. The stimulus was not only not recognized, but treated as if it did not exist. This disorder pertained also to dress, to the left side of the body, and to the left side of space. Indeed, when testing temperature sensation with the eyes closed, a small applicator so hot as to redden the skin was ignored. This might erroneously be thought to be an "asymboly for pain."

The phenomenon of suppression of perception of a single stimulus on the affected side of the body by a concurrent stimulation on the normal side was present in remarkable degree. It was also present in relation to one of any two stimuli simultaneously applied on the left side. There was a constant tendency of stimuli in the face on the left side to suppress others in the left arm, and for the left leg to dominate other parts of the left limbs. The persistent dominance of the right side was clearly different only in degree from the dominance of some parts of the left

side. In the fields of vision the right half-fields also showed a persistent dominance in this sense. In the left half-field two stimuli exhibited failure to register as two only if small enough and distinct enough (two small points of light). Two large objects in the left field were perceived as two, and the tachistoscope showed that speed of perception of a single stimulus was not altered in either field.

The importance of the size of the visual stimulus in relation to extinction led us to estimate the effect of quantitative differences between dominant and suppressed stimulation. It was then found that if a sufficient number of pricks was delivered on the left side, the resulting sensation could not be suppressed by the previously dominant stimulus. Just as the differences between single stimulation on the two sides could be compensated by quantitative increase on the left, so dominance could be overcome by quantitative increase. Further, the degree of quantitative increase necessary to dominate suppression could express the degree of dominance.

These findings appear to us to force a revision of conceptions of the contribution of the parietal lobe to sensory perception. The conclusion of Head and Holmes (1911) and Head (1920) that disorder of sensation from parietal lesions differs from all other forms of sensory change in the absence of change in threshold of point stimulation of the skin can be readily verified in any disorder of cortical sensation. A touch or a prick or a two-point sensation is perceived, or not; the percentage of errors is not materially lessened by increasing the strength of stimulus. The response is an all-or-none discrimination. Head and Holmes comment that the patient frequently reported the sensation, if perceived, as "less plain" than that of the normal side, but do not discuss this difference except to state that it "exhibits the characteristic confusion and want of definition seen in cortical lesions." The effect of increase in number of points stimulated does not appear to have been explored in this respect, except that the phenomenon of loss of two-point discrimination, intensively studied by Head and Holmes, was viewed as the loss of a predicated property of spatial discrimination. That the single perception from such double stimulation was more distinct, more plain than the single stimulus alone, appears to have escaped notice. Yet dominance and extinction are clearly related to the relative degrees of lack of clarity of perception of the single stimulus.

A stimulus on the left side was insecure even when alone. It gained recognition only by virtue of its intensity, area, and high differentiation from the left environment. The order of dominance of different parts of the left side paralleled the disorder of spatial discrimination (two-point), appreciation of temperature, and tactile localization in these parts. Within the left side the competition of two stimuli for recognition must therefore be a secondary process by which the same factors operate between the two stimuli as between either stimulus alone and the back-

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ground environment. On the right side two stimuli evidently stood clearly perceived as two distinct but concurrent events. On the left side every aspect of the differential mechanism was impaired so that a conclusion could be reached regarding only a few elementary properties. In regard to the presence or absence of a touch, or a prick, a single left stimulus would appear to have been well perceived, but double stimulation clearly shows that spatial orientation, multiplicity of components (including roughness of surface) and other comparative differentiations within the double stimulus, is a more difficult, and hence more vulnerable cortical process. Up to this point we find ourselves in agreement with Bender and Teuber (1948) and Wortis, Bender and Teuber (1948) that "extinction" is preferable to "inattention" in description of the phenomenon, and that "abnormal gradients of excitability" are necessary for the appearance of extinction, though we would prefer to speak of gradients of discriminative ability. Attention implies an unknown process with selective properties. "Inattention" in this sense is difficult to apply to the left side of the percept itself. If the phenomenon of extinction is directly related to vulnerability of the known properties of the stimulus it is the result of rivalry for recognition at some level of perception.

The evidence presented by our patient appears to indicate clearly that the phenomenon called "extinction" of one member of a double stimulus is not due to direct interaction between one stimulus and another. The peculiar time-relationship for extinction, which requires that the extinguishable stimulus succeed the first within a period of 3 seconds, indicates that a unitary process within that period of time is involved. When the more abnormal stimulus is repetitive it may not be recognized for as long as 30 seconds after the competing stimulus, but it was evident that after the first 3 seconds the phenomenon is relative in degree and more and more easily broken down by reinforcement or by attention. Within this period the better discrimination is detrimental to the survival of the lesser. This time-relationship is of great interest. There is no defect in temporal summation in the sense of cumulative effect of repetition of the same stimulus. It will be noted that the first stimulus establishes a perceptual event with a definite time-interval. If the impaired stimulus is first it must reach beyond the point of vulnerability. If it is second it is vulnerable in a time-interval pertaining to the first stimulus. Therefore at some step in the chain of events leading to perception a stimulus must interact with any immediately preceding stimulus before it enters perception. The two stimuli do not summate in time to produce a third, mixed perception. Instead, two or more stimuli presented to the cortex within this period are treated as one perceptual event, *as one total stimulus*, and the differentiation of its component parts becomes another factor, more complex and more vulnerable than the differentiation of each part alone from the environ-

ment. With a certain degree of impairment of the cortical mechanism, only the component with the most highly differentiated properties is perceived.

Of two stimuli applied to the left side one applied to the leg could dominate another applied to the arm, whereas one applied to the face could dominate one applied to the arm or leg. Cohn (1951) has found that in children under the age of six years a cephalocaudal gradient of dominance of double stimulation normally exists. Bender, Shapiro and Schappell (1949) have noted that the foot commonly dominates the hand, and the face both hand and foot, in a whole series of hemiplegias, so that it is doubtful if the order of dominance depends on anatomical factors. In our experience the phenomenon of extinction can be regularly demonstrated whenever an area of skin surface is sufficiently affected to produce evidence of loss of two-point discrimination, with or without other evidence of cortical sensory damage. Some ability to distinguish two-point sensation in the face may eventually recover after hemispherectomy (Bell and Karnosh, 1949) so that the bilateral sensory mechanism of discrimination for the face and mouth probably determines the dominance of that area in complete parietal lesions. The regularity with which the hand is subordinated to the foot in a variety of types of hemisphere lesions implies a more specialized function of the hand in normal perception.

There are therefore two distinct kinds of imperception of simple cutaneous stimuli resulting from a cortical parietal lesion, the first an inability to perceive a single stimulus such as a very small area of temperature change, or a certain proportion of a series of touches by single hair or pricks with a single pin. The second is the inability to perceive the less differentiated of a pair or larger number of concurrent stimuli. The degree of disorder of the first type of perception is parallel to the degree of disturbance of the second. The first was directly associated with the more complex disorder of tactile astereognosis, the second exhibits in simple form the conditions for extinction of visual recognition in the left field. Both tactile and visual perception exhibited the same phenomena in different degrees.

The most elementary degrees of these disorders, as well as the most complex, exhibit defect in spatial summation. This is particularly evident in the defect in appreciation of intensity of temperature, which is the greater the smaller the area stimulated. Weber recognized that the sensitivity of perception of temperature was greatly increased with increase in area of stimulus, and more recent studies (Hardy and Oppel, 1937) have shown conclusively that spatial summation is a striking feature of normal perception of thermal intensity. The threshold of perception of pressure, touch and visual stimuli and the normal appreciation of their intensities is likewise dependent upon spatial summation (Boring, 1942). Perception of pain alone normally fails to show evidence of spatial

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summation (Hardy, Wolff and Goodell, 1940). In the disorder produced by parietal lesions, however, the perception of pain, as in our patient, clearly exhibits a spatial summation. Inability to demonstrate this in the normal may be only the result of greater overlap of the peripheral units of pain sensibility than is the case of other sensations. Certainly spatial summation is normally most apparent in perception of heat, for which the end organs are most separate. The existence of spatial summation in normal perception of temperature requires ranges of effective stimulation of end-organs individually or in groups which do not result in any perception. As a result of parietal cortical lesion this range of ineffective stimulation is greatly increased. This indicates that spatial factors are an essential ingredient in all sensory recognition; that without a spatial element there would be no perception. In the more complex discriminations served by the parietal cortex the synthesis of spatial factors is evident, and tactile astereognosis is a prominent example. The defect in discrimination of multiple visual and auditory stimuli also betrays this reliance on spatial synthesis. The defect in appreciation of posture and of weights implies an inability to perceive spatial data relating to the organism itself, or forces tending to disturb these. We therefore conclude that the disturbance of function presented by right parietal lesion implies that the parietal lobe is primarily concerned with the spatial summation of sensation.

In all partial degrees of loss of spatial summation in perception the phenomenon of extinction is prominent, and this was found to be dependent upon what might be called the unity of the perceptual process. Spatial summation of some degree being achieved, completion of perception then depended upon rivalry within a mechanism which could be blocked for periods of 3 or more seconds by a more highly differentiated competitor. Impairment of spatial summation was accentuated when it entered a second frame of reference, namely that of time. Here there is not a space-time continuum, but a series of overlapping static time periods of 3–30 seconds. The cephalic dominance of children indicates that priority in time is of value in normal perception. The study by Duncker (1937) of rivalry of two pain stimuli for recognition also indicates that features of this temporal unity exist in the normal individual. Our findings therefore lead to the conclusion that defect in spatial discrimination resulting from parietal lesion is accentuated by the normal unity of the temporal frame of reference. Spatial summation is a primary element in perception; temporal summation is a secondary process involving a further heightening of discriminatory function. There is no evidence that temporal summation is damaged by parietal lesion.

The Nature of Imperception and Agnosia

The impairment of perception resulting from peripheral lesions, and from central tract lesions up to and including the thalamic level, is

proportional to the demonstrable raising of threshold of appreciation. Disorder of perception of spatial attributes also then can be directly related to change of threshold. The result of parietal lesion is unique in that strength of stimulus is a subsidiary factor, so that whether the stimulus is perceived or not is dependent upon other factors. The most important determinant is now the spatial attribute, whether the stimulus covers a large area or small or is multiple rather than single. The next most important determinant is the relationship between this aspect of the stimulus and that of any other stimulus that may be competing for recognition. The spatial defects of parietal lobe syndromes have been emphasized by almost every writer. Disorientation in space, and loss of sense of space have been frequently reported to result from lesions of the left parietal lobe. Lange (1930) attributes finger agnosia to disturbance of direction in space. It has been maintained by Goldstein and Gelb (1918), Schilder (1935), Lhermitte and Trelles (1933) and others that a sense of space depends upon a combination of tactile, proprioceptive and visual perceptions, in such a way that it is incompletely perceived by any one of these alone. The most simple form of disturbance has been assumed to be tactile astereognosis, now termed "parietal tactile agnosia" (Neilsen, 1936). The word agnosia "proposed by Freud to signify loss of ability to recognize objects, has been extended to signify loss of symbols as well through one sense organ, the loss being due to a cerebral lesion, and general mental defect excluded as cause, relative intactness of the sense in question retained, and the object or symbol being recognizable through some other sense organ" (Neilsen 1936, p. 165). Agnosia in this classical sense is equivalent to the "imperception" of Jackson. Yet in our patient we find every transition from defect in the perception of the most simple spatial qualities of stimulus to the lack of recognition of the multiple features that characterize an object. We conclude that even in its most simple forms, the appreciation of temperature or pain, or extinction of one of two stimuli, disorder of perception has some of the physiological characteristics of agnosia. Yet, since current terms have been defined in terms of symbols and objects, and have accepted connotations in the psychological approach to these disorders, we have sought a term to convey the special physiological importance of spatial summation in the function of the parietal lobe. We propose to employ the term *morphosynthesis* for the various physiological forms of cortical spatial summation.

It is generally accepted since the work of Russel and Horsley (1906), Déjerine (1914) and Head (1918) that a cerebral lesion may lead to a relatively localized loss of tactile localization and two-point discrimination in, for example, an area confined to the hand, or even the ulnar or radial border of the hand, the other parts being unaffected. To this extent the damage to projection of sensation to the sensory cortex gives evidence of the segmental pattern of representation of parts of the body on the

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post-central gyrus. When the sensory disturbance lies in the radial border of the hand, as in some cases of localized cortical injury, astereognosis is not a symptom. It has therefore been assumed by some that astereognosis and other types of agnosia are derived from lesions of more posterior parts of the parietal lobe. We doubt if this is the case, for it is apparent that the methods of testing for astereognosis are not such as to demonstrate a defect on the ulnar or radial border of the hand alone. When two-point sensation is lost in the whole hand, astereognosis is present. We are unable to find evidence to show any difference in the *type* of loss of discrimination depending on the part of the right parietal lobe that is damaged, irrespective of the sense involved. Larger lesions result particularly in loss of more comprehensive spatial perception, but it is equally apparent that larger distribution of discriminative aspects of sensation is necessary for spatial discriminations to be made. The shape of an object cannot be judged by one touch spot any more than the position of a limb in space can be judged by one joint receptor. Head (1920, p. 692) was much concerned with differences in the relative degrees of disorder of tactile recognition, spatial localization, and of posture, and the appreciation of weights, in different patients. Though he recognized that these functions were interrelated, he was unable to arrange them in a graduated scale of increasing complexity, of increasing vulnerability to cortical lesion. He therefore viewed these categories of disorder as reflections of independent divisions of cortical function. We should not be misled by different accentuations in terms of anatomical factors into thinking that the natural function is thus subdivided. It now appears probable that the area of arrival of the proprioceptive contribution to the parietal cortex is not exactly coterminous with the tactile influx, so that it is possible for a function depending on both to be affected preponderantly in terms of one or other. It has recently become clear that pain is not referred to the same areas as touch (Marshall, 1951). The addition of symptoms relating to extra-personal space must require a difficulty in discrimination of visual sensory data, and hence an extension of the lesion to the more posterior parietal region.

The patient we have reported in detail in this paper presented a severe degree of disorder of spatial summation in relation to all forms of sensation from the left side, without the complication of defect attributable to damage to any one of the conducting subcortical pathways. We have observed many others with such defects in addition, at various levels of the sensory projections. "Astereognosis," for example, can readily be demonstrated in suitable partial lesions of peripheral nerves, spinal cord and brain-stem. Extinction and loss of two-point discrimination are prominent under the same circumstances. The associated disorder of threshold for perception of the primary sensations then fully explains the added defects in perceptual synthesis. Similarly, partial lesions of the optic radiation or calcarine cortex may result in defects in spatial

perception in partially affected portions of the visual field. Such perceptual defects are secondary to numerical reduction in primary sense data. Only when the perceptual disorder stands apart from defect in primary sense data does it indicate damage to parietal cortex. In this respect it is important to distinguish clearly between inability to distinguish a proportion of touches, pricks, points of light, etc., on the affected side, resulting from defective spatial summation, from the raising of threshold and loss of sensation resulting from peripheral, tract, or radiation lesions.

We are therefore led to the conclusion that all the parietal cortex is concerned in spatial sensory discriminations. When this function is disturbed in terms of both general sensation and vision, there appear the disorders of perception of the opposite half of environment and person which are characteristically shown by our patient. We view these disorders, as well as the phenomenon of cortical "extinction," and related defects in appreciation of intensity as aspects of the general phenomenon of *amorphosynthesis*. Though visual aspects of the disorder arise more particularly in relation to damage to the posterior parts of the parietal lobe, and auditory effects require a more complete lesion, we find no reason to postulate a parcellation of the function of morphosynthesis itself. Such visual, auditory or other accentuations may represent only relative preponderance of lesion in the region of arrival of one or other of incoming pathways. The visual disorder in our patient was profound, but it notably lacks the absolute failure of recognition which is characteristic of the specific visual agnosias of the dominant hemisphere. The type of visual defect in our patient is of a lower, more general, order. A large enough, obvious enough, stimulus of any shape could break down the difficulty and claim visual recognition. The tactile astereognosis could be abolished by the co-operation of the left field of vision, itself defective in the same sense. Tactile astereognosis as ordinarily understood is what we would call tactile amorphosynthesis and the confusion between perception and recognition implied by stereognosis makes this word undesirable. In the more complete disorders of the right parietal mechanism, lack of appreciation of extra-personal space and disorder of dressing imply only a more complete inability to circumscribe a stimulus from the left side.

If all these disorders are the result of damage to a parietal half-centre for perception, they should also occur in the right side following left parietal lesion. They are found to be present if especially sought. Their one-sidedness in patients such as ours makes it inconceivable to us that the right parietal region has some special, unique significance in regard to visual space perception, a view tentatively suggested by McFie, Piercy and Zangwill (1950). The more simple disorders that we have discussed, namely extinction, loss of tactile and postural discrimination, and astereognosis are well known to be present in the right side in left parietal lesions. The aphasia and complex agnosia associated with left

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parietal lesions obscures many of the visual morphosynthetic features. Indeed, as Paterson and Zangwill (1944) point out, the disorders in left visual space in their patient are closely paralleled by some details of semantic aphasia as described by Head (1926) in cases of left parietal lesion. Within the greater disorder of classical visual agnosia, as in a case reported from our clinic by Adler (1944), the patient confuses the letters P, B, and R, and the letters F and E, and in other ways indicates greater difficulty to the right side. Thus the general defect in visual imagery and propositional speech in left hemisphere lesions may overlay and obscure the unilateral symptoms converse to right hemisphere lesions. Bilateral lesion of the posterior parietal region can produce absence of visual orientation in space, and ability to recognize only one object at a time, without agnosia as in the cases described by Holmes (1918). We imagine this disorder to represent bilateral amorphosynthesis. The case described by Smith and Holmes (1916) is particularly interesting in this connexion, because topographic memory was preserved.

Head (1926) has shown the interdependence of speech, mental imagery and thought. Each of these is contaminated with certain features of the others, the common elements being symbolic formulation and conception. The disorders which are recognized as associated with damage to the dominant hemisphere all involve defects in symbolic formulation in its widest sense. Many writers have endeavoured to stress two factors in visual perception, the act of perception of a sensory impression ("apperception" of Lissauer, 1889), and an act of linkage of simple perception with other images ("association," Lissauer). We do not find such distinctions of value in relation to the defect from right hemisphere lesion. A physiological analysis of agnosia based on the assumption that the usual features of right parietal lesions is the fundamental pattern of primary hemispheric sensory discrimination at once greatly simplifies the various arbitrary phenomenological classifications of agnosia. Thus we would view all the disorders presented by our patient as amorphosynthesis in its broadest sense, and all those disorders which are peculiarly the result of the damage to the dominant hemispheres as symbolic agnosias. Amorphosynthesis is subject to infinite gradations, and is strictly contralateral. A symbolic agnosia is absolute within its special conceptual category, and is bilateral from unilateral lesion. We consider this differentiation to be essential to the physiological approach to cortical perceptive processes.

The question raised by Roth (1949) as to the reason for the difficulty in recognition of the whole left side of the body in right hemisphere lesions, and of the fingers in left lesions, clearly exemplifies the difference we seek to establish between amorphosynthesis and symbolic agnosia. These defects are not comparable. The first is an admission by the patient or a betrayal in his behaviour; the part or whole side is, for its usual purpose, regarded as non-existent. The second is a response to naming, or to an

order given by the examiner, or to a pictured representation, and the patient fails to reach the required conception of the part or the whole. The first is the failure of a cortical stimulus, most evident in failure to react to something on the one side. The second is a difficulty in the mental manipulation of a conception of a thumb, a finger, or a digit applicable to both sides. Denial of the left side of the body is not the maximum of defect which begins as finger agnosia. Denial of the left side of the body begins with left-sided loss of sense of posture and tactile localization. Conversely, the maximum of finger agnosia, as seen when a parietal tumour progresses, is disorientation of person. For this reason we have up to this point avoided all reference to the "body image," for we regard the conception of "body image" which Schilder (1935) so illuminatingly develops from the "postural model" of Head and Holmes, as a symbolic concept peculiarly significant for the dominant hemisphere. The manner in which the patient ignores the left side in right hemisphere lesion is a distortion of behaviour; the body image in the patient's mind is intact. Cases such as that in Pinéas (1931) in which there was a difficulty in naming parts of another person as well as denial of the left side of the body also suffered from aphasia and memory defect. Head's "schemata" were more simple and predicate an unconscious background reference derived from previous sensations without which alterations in sensations could not be appreciated.

The postulate of "schema" in this sense was an attempt to explain the loss of sensory discrimination without affection of perception of primary sensation. We find, however, that the primary sensation is indeed altered, is "less plain" in the words of the patients of Head and Holmes. Discrimination and perception suffer equally together. It is agreed that a continuum of sensation is necessary in order that a new sensation should have a reference point, but this requires only a threshold quantity of general sensation. The postulate of a schema is not necessary. The situation in which the patient can localize touch and know which particular spot on the arm has been touched, but is unable to determine the position of the arm in space, is used by Head to prove that the postural schema is based on posture. Schilder points out that an optic "schema," or "image of the body" is then still present, to which perception could be referred. This appears to us to confuse the terms, for we would consider the sensory data for postural morphosynthesis defective, while the concept of body and parts of body to be unaffected. We believe, moreover, that a complete body image can be present without any sensation from the left side, and is shown by ability to indicate parts of a diagram or mannikin. It is essential to review methods of testing to make sure that a defect in conception does not interfere with a defect in perception, and vice versa. There is no evidence that in this sense a second step in the process of perception is specially vulnerable in lesions of the non-dominant hemisphere. When difficulty in naming and

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identifying fingers has been present with a right parietal lesion, as in Case 2 of Roth (1949), it has been an added difficulty in visual concept, applicable to both hands, and not applicable to eyes, nose, shoulder or trunk, or to five matchsticks. "Inability to relate the stimulus to a schema of his hand" (Roth) in this sense is what we would call a disorder of symbolic function, and predicates a dominance of the right hemisphere in this respect in Roth's patient.

The disorders of visual spatial perception resulting from uncomplicated right parietal lesion are particularly instructive. The left side of space has contracted in physiological significance and becomes liable to extinction by an event in the right side of space. Defective visual localization of objects in space in the presence of good visual acuity (*Ortsblindheit*) was distinguished by Kleist (1922) from agnosias for visual space. We would make the same distinction between visual amorphosynthesis, a unilateral defect in the perception of spatial relationships, and topographic disorientation, a bilateral agnosia for topographic imagery. Visual amorphosynthesis clearly varies in degree in different patients, and can be caused by extinction to fluctuate from time to time in the same patient. Confusion of right turns with left in route finding in right hemisphere lesion, for example, is the result of left extinction and left amorphosynthesis, and its prominence in some patients and not in others is for us an index of severity of the disorder. To categorize these mistakes in route finding as "agnosia for the left half of space" (Brain, 1941*b*) does not take account of the physiological factors in perception. The separate classification of a whole series of variants in the phenomenology of amorphosynthesis as separate agnosias has led by inference to the postulation of a whole series of perceptive functions. The reported lesions for such variants of agnosia as have been listed by Pötzl (1928), Brain (1941*b*), and Neilsen (1940) are remarkably similar, and we doubt if such functions exist.

The disturbance of visual orientation reported by Holmes (1918, 1919) to result from bilateral parietal lesion exemplifies bilateral visual amorphosynthesis. It should be sharply distinguished from topographic disorientation of the type described by Paterson and Zangwill (1945) which portrays agnosia for topographic conception, usually associated with defective topographic memory. Such topographic agnosia has complicated visual amorphosynthesis from right parieto-occipital lesions sufficiently frequently (Paterson and Zangwill, 1945; Neilsen, 1940) to make it apparent that right parietal dominance may occur in right-handed persons.

The disorders resulting from damage to the right parietal region, as exemplified in our patient, are distinct from the defect in a patient with hemianæsthesia resulting from right thalamic lesion, with or without hemianopia. The patient may then initially deny the existence of the defective side, but a process of learning to use the remaining side to

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explore the imperceived field rapidly begins. The striking feature of the unilateral cortical parietal syndrome presented by patients such as reported here is the continued behaviour as if the affected side, and half of space, did not exist. This is characteristic of a defect in perception, as opposed to a mere loss of sensation. There is no spontaneous attempt to explore the affected side with the sound sensory field. This is seen in the defect in construction of models, of drawings, in dressing, and very clearly in our patient in the lack of recognition of objects in the left half of a composite picture of many objects. Such inattention to the left half of space and of person is not reported to follow hemispherectomy. The absence of any process of learning to use the right side to explore the left in eleven months in our patient emphasizes this distinct feature of parietal lesion. Some perceptive factor on the affected side must be sufficient to allay interest. The phenomenon of unequal bisection of lines and figures indicates that the affected field is perceived but is less significant in size. We have found this a simple and reliable test for a unilateral perception defect. Defective localization of touch is stated by Head and Holmes (1911, p. 162) to be usually proximal to the point stimulated, and they remark on the resemblance between this ideational foreshortening of the limb resulting from cortical lesion and the shortening of phantom limbs. As shown by our fig. 4, this false reference is more complex, though its effect is to foreshorten the upper arm and leg, and focus the limbs at wrist and ankle. The unequal bisection of lines reveals that all perception on the affected side is less spatially significant. The corresponding behavioural defect gives objective measure of the parallel loss of stimulus value. Inattention to the left field and apraxia of dressing indicate not the loss of a category of function but the diminution in biological stimulus value in the left exteroceptive field. We consider that anosognosia, when it occurs, is derived from this same physiological disorder, for it lacks the conceptual features of pure agnosias, is one-sided, and is regularly associated with cortical sensory loss (Pinéas, 1926), i.e. with amorphosynthesis. Its occurrence with large parietal lesions indicates that a combination of visual with other elements of amorphosynthesis is necessary, and that loss of cortical sensation in the limbs is not necessarily maximal.

The presence of unresolved perception, independent of awareness, is also shown by the automatic sensorimotor reactions present on the left side, such as the curious phenomenon of involuntary raising and extension of the left hand and wrist whenever an examiner approached the patient from the left, regardless of the direction of interest of the patient at the time. This phenomenon was visual, but could be reinforced by tactile stimulation in the sense that light touch on the hand made it rise higher. The unawareness of the patient was indicated by her embarrassment and natural replacement of the hand whenever her attention was drawn to its strange posture. We have noticed this phenomenon in other cases of

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parietal lesion, and Schilder (1935) mentions it in one of his cases. The presence of this complex, but unconscious, reaction indicates that right cortical automatisms could function independently, and perhaps in this way fulfil a function which a more completely hemianæsthetic nervous system would attempt to compensate with the other hemisphere. We would therefore conclude that the peculiar indifference to the left side of person and extra-personal space in our patient is due to the lack of stimulus value of a poorly resolved cortical reaction on that side associated with a partly dissociated motor reaction. The "levitation" and involuntary posture assumed by the left upper limb was such as if to avoid an object approaching from the left side. The hand regularly tended to assume this posture when outstretched (fig. 2). Lhermitte and his associates (1925, 1928) refer to similar abnormal attitudes in their patients as an apraxia. We would regard the phenomenon as a released cortical visual automatism, acting independently of the rest of behaviour. In this sense it is directly comparable to the release of the grasp reflex by frontal lobe lesions. Our patient also showed an apraxia of the type commonly called "constructive apraxia" (following Pick) and "apraxia for dressing" (Brain, 1941*b*), but the defect in movement was then patently the direct result of failure of perception of the next step in a movement sequence.

The most obvious defect in patients with right parietal lesion is in relation to behaviour. Our patient behaved either as if the left environment was not present, or else her performance in relation to her left side was incomplete. This indicates clearly that morphosynthesis is primarily functional in objective. A chair is something upon which to sit, a sleeve is something with which to cover the arm, a cup is something from which to drink. Recognition is part and parcel of behaviour. In right parietal lesion, if an object is recognized, its symbolic significance can immediately be deduced. A coin, if recognized, can be named; a word, if read, is fully appreciated. If recognition fails, symbolic significance is absent. In patients with parietal lesion in the dominant hemisphere the symbolic significance of the object may be lost, though its functional significance in terms of behaviour be unimpaired. Of course behaviour based upon the defective formulation of the conception will then be impaired, but special tests may be required to show this. The defect is then more obvious in the patient's interpretation than in his general behaviour. Nevertheless, since defect in motor performance is inevitable in some degree in both agnosia and amorphosynthesis, such defects could be called psychological and physiological ideational apraxia respectively. On similar principles Goldstein (1923) differentiates abstract and concrete behaviour. A patient who could go through the movements of drinking from a glass only if it was filled with water (Goldstein and Gelb, 1920; Goldstein, 1923) is a classic example of the fundamental difference which we emphasize. The essential defect is, however, in the process of

recognition and for that reason we refer all such disorders to one or other of the two disturbances of perception; either bilateral psychological conceptual agnosia, or a unilateral physiological amorphosynthesis. We would agree with Lange (1936) that ideational apraxia cannot be separated from defects in perception.

In this way it appears possible to explain the clinical phenomena of right parietal lesion in physiological terms, that is, in terms of a disorder in the perceptual synthesis of the spatial aspects of sensory data. It is possible to account for the spatial aspects of these disorders without reference to a sense of space. Yet such an approach more clearly defines the properties of sense of space and sense of person, and emphasizes their peculiar symbolic imagery. It is apparent, however, that in the past confusion has arisen from failure to distinguish sharply between phenomena resulting from failure of unilateral perception and inability to recognize conceptual schemata whether drawn in outline, pictured in imagery, or conveyed to the patient in speech (agnosia, aphasia). Thus we find reason to doubt the existence of any disorder of the conception of the patient's own body or of extra-personal space or of topographic representation in the patient's mind as a result of lesion on the non-dominant side, though his behaviour and comprehension may be disordered in relation to all these. When these concepts are disordered by a lesion on the dominant side very specific defects result. We feel certain that further study of amorphosynthesis will enable tests for agnosia to be devised which are free from contamination by the more simple defects of perception, and thus throw the mechanism of symbolism into clearer perspective. For example, the fragmentation of the efforts of the patient to draw a picture of an object or a symbol has been commented upon by many writers. This is the "discontinuity" of Head (1926), and the "piecemeal procedure" of Paterson and Zangwill (1944). It is clearly derived from the singleness of disordered perception, and the related phenomenon of "extinction." The patient can only perceive one item at a time, and if that item is the line he has drawn he manifestly cannot also perceive the whole that he tried to complete. Perception of one tree prevents him from seeing the wood. This unity of reduced perception also must underlie the constriction of visual fields commonly found in patients with visual agnosia (Goldstein and Gelb, 1918; Goldstein, 1943) for, although the patient may perceive objects at the periphery of the field of vision, any attempt to chart the field by conventional methods of fixation on a central point will result in extinction of the more peripheral stimulus. Such constriction is the result of the method of charting the visual field, and is of no significance regarding acuity at the periphery of the field.

Similarly the preoccupation of the patient with some small part of the pattern, with inability to deduce the whole from the nature of such small parts, has led to the Gestalt theory of visual perception. The ability

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of the patient sometimes to recognize the whole without ability to deduce it from perception of separate parts has been held to confirm the importance of gestalten (Conrad, 1932). But these phenomena are also the result of the method employed, and only demonstrate the unity of the reduced morphosynthesis. As Piéron (1929) has remarked, the process of recognition is extremely rapid, is built on very simple patterns, and is not comparable with the intellectual procedure of deduction. We therefore doubt if the concepts of "structuration" (Conrad, 1932), or of gestalten in any sense other than patterns in imagery, are useful in the better understanding of disorders of perception.

The recognition of the symbolic or conceptual features of an object must depend primarily upon the recognition of its concrete qualities. In the dominant hemisphere the anatomical structure concerned in the recognition of symbolic features is likely to be closely related to that for morphosynthesis. The very specific nature of agnosias indicates, however, that the mechanisms concerned in symbolic recognition are more vulnerable to injury than the more simple process that underlies it. This vulnerability may be related to fibre connexion to the related areas for speech and revisualization. We find no reason to suppose that either figure or background are specially vulnerable in morphosynthesis. If the perceptual whole is more than the sum of its parts this may mean only that the total conception is greater than the percept which arouses it (Brain, 1941*a*). The physiological attributes of perception accompany the psychological wherever cerebral function has a conceptual component. They manifest themselves, for example, in the difference between interjectional and propositional speech, resulting from lesions far removed from the parietal lobe.

Of the many problems presented by the physiology of perception two present special difficulties. One is the nature of the process we call "attention," and the other is the anatomical location of that general background of perception that is called awareness. Attention is closely associated with awareness, but has a labile quality which suggests that it is an epiphenomenon. Attention was seemingly unaffected in our patient, except that its application to the left side was transitory, was chiefly effective in visual recognition, and could overcome the extinction of only slight rivalry in the unaffected field. The fundamental defect was deeper, and independent of this "inattention." In our patient a change in total personality variously described as "indifference" or "placidity" was particularly noticeable. The patient was not apathetic; she maintained a superficial interest in watching what went on around her. But her attitude was entirely passive; she lacked initiative. There was no demonstrable dementia, and memory function was excellent. It is therefore possible that total awareness was reduced in its more subtle aspects, though we could not estimate the degree of this. The singleness of awareness, or consciousness, is an even greater problem in

the physiological understanding of mind. It is necessary to point out that if, as Hughlings Jackson maintained, consciousness or awareness is a by-product of cortical sensorimotor processes, a unilateral constriction of awareness would necessarily follow damage to one side of a bilateral organ concerned in it. Our patient showed just such a reduction in consequence of a unilateral parietal lesion. Yet within the total area of awareness perception behaved as a unitary fragment, exhibited within either right or left field, with a total duration of about 3 seconds, and with traces lasting to 30 seconds. In this interval of time any stimulus or combination of stimuli was treated as a unit percept, within which various subordinate factors such as multiplicity, intensity and extent could be separately differentiated. It is therefore concluded that the unity of the perceptual field is an illusion, that it has two halves which can each be damaged independently. The unit function would then be the facilitator which is called attention, which is attached more particularly to the temporal sequence of the perceptual process.

Conclusions

(1) Study of a patient showing disorders in perception of two stimuli, of the left side of extra-personal space, of person and of personal dress, and of the discriminative aspects of sensation on the left side, as a result of a right parietal vascular lesion without aphasia or hemiplegia, gave evidence that all these perceptual disturbances were interrelated.

(2) The phenomenon of extinction of perception of one of a stimulus pair was found to be directly related to the degree of difficulty in differentiating the properties of the extinguished stimulus when alone. The defect is in terms of spatial summation, and may not be obvious with the single stimulus alone.

(3) When acuity of perception is reduced, each combination of stimuli is treated as a unitary whole, within which poorly differentiated features are eliminated in rivalry with those better perceived. The unitary process appears to be a normal event in perception, related to attention, and its effect is to amplify defects of spatial summation.

(4) The parietal cortex is concerned in the first stage of perception, spatial summation, and its function is the recognition of form ("morphosynthesis"). This is a physiological process with correlated behavioural aspects. Its defects ("amorphosynthesis") are one-sided, relative in degree, and associated with corresponding apraxia. The less complex, and probably all, the manifestations of loss of spatial summation of contralateral sensation resulting from parietal cortical lesion, can be present in left-sided lesions as well as right. Amorphosynthesis should be sharply distinguished from the absolute, bilateral special agnosias resulting from lesions of the conceptual mechanism of the dominant hemisphere.

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(5) The loss of visual components of such "morphosynthesis" in addition to tactile factors, is the basis of unawareness of part of extrapersonal space and unawareness of self, without disorder of the concept of space or of body schema. Such unawareness differs considerably from simple loss of sensation.

(6) The defect in motor behaviour resulting from parietal lesions is the result of lessening of adequacy of stimulus for cortical reactions. Some simple cortical automatisms such as avoiding of contact with external objects undergo transcortical release, partly dissociated from awareness.

REFERENCES

ADLER, A. (1944) *Arch. Neurol. Psychiat., Chicago*, **51**, 243–259.

BELL, E., and KARNOSH, L. J. (1949) *J. Neurosurg.*, **6**, 285–293.

BENDER, M. B. (1945) *Arch. Neurol. Psychiat., Chicago*, **54**, 1–9.

—— (1946) *Arch. Neurol. Psychiat., Chicago*, **55**, 299–329.

——, and FURLOW, L. T. (1945) *Arch. Neurol. Psychiat., Chicago*, **53**, 29–33.

——, and TEUBER, H. L. (1946) *Arch. Neurol. Psychiat., Chicago*, **55**, 627–658.

——, —— (1948) *Arch. Neurol. Psychiat., Chicago*, **59**, 39–62.

——, FINK, M., and GREEN, M. (1951) *Arch. Neurol. Psychiat., Chicago*, **66**, 355–362.

——, SHAPIRO, M. F., and SCHAPPELL, A. W. (1949) *Arch. Neurol. Psychiat., Chicago*, **62**, 717–724.

BORING, E. G. (1942) Sensation and Perception in the History of Experimental Psychology, New York (Appleton-Century).

BRAIN, W. R. (1941*a*) *Brain*, **64**, 43–62.

—— (1941*b*) *Brain*, **64**, 244–272.

COHN, R. (1951) *Neurology*, **1**, 119–122.

CONRAD, K. (1932) *Mschr. Psychiat. Neurol.*, **84**, 28–97.

CRITCHLEY, M. (1949) *Brain*, **72**, 538–561.

DÉJERINE, J. (1914) Sémiologie des Affections du Systéme Nerveux. Paris (Masson).

DUNCKER, K. (1937) *Psychol. Forsch.*, **21**, 311–326.

FURMANSKI, A. R. (1950) *Arch. Neurol. Psychiat., Chicago*, **63**, 205–217.

GOLDSTEIN, K. (1923) *Mschr. Psychiat. Neurol.*, **54**, 141–194.

—— (1943) *J. Nerv. Ment. Dis.*, **98**, 148–153.

——, and GELB, A. (1918) *A. ges. Neurol. Psychiat.*, **41**, 1–142.

——, —— (1920) *Z. Psychol. Physiol. Sinnesorg.*, **83**, 1.

——, and SHEERER, M. (1941) Abstract and Concrete Behavior, Psychol. Monogr. **53**, No. 2, 1–151.

GRUNBAUM, A. A. (1930) *Z. ges. Neurol. Psychiat.*, **130**, 385–412.

HARDY, J. D., and OPPEL, T. W. (1937) *J. Clin. Invest.*, **16**, 533–540.

——, WOLFF, H. G., and GOODELL, H. (1940) *J. Clin. Invest.*, **19**, 649–657.

HEAD, H. (1918) *Brain*, **41**, 57–253.

—— (1920) Studies in Neurology, Vol. 2, London (Oxford Med. Publ.).

—— (1926) Aphasia and Kindred Disorders of Speech. London (Cambridge Univ. Press).

——, and HOLMES, G. (1911) *Brain*, **34**, 102–254.

HOLMES, G. (1918) *Brit. J. Ophthalmol.*, **2**, 450–516.

—— (1919) *Brit. Med. J.*, **2**, 230–233.

KLEIST, K. (1922) *Handbuch der aerztl. Erfahr. im Weltkreige*, **4**, 343.

LANGE, J. (1930) *Mschr. Psychiat. Neurol.*, **76**, 129–188.

—— (1936) Agnosien und Apraxia, in Vol. 6 of *Handbuch der Neurologie*, ed. Bumke and Foerster, Berlin (Springer).

LHERMITTE, J., LÉVY, G., and KYRIACO, N. (1925) *Rev. Neurol.*, **2**, 586–600.
——, DE MASSARY, and KYRIACO, N. (1928) *Rev. Neurol.*, **2**, 895–903.
——, and TRELLES, J. O. (1933) *L'Encephale*, **28**, 413–444.
LISSAUER, H. (1889) *Arch. Psychiat. Nervenkr.*, **21**, 222.
MAAS, O. (1910) *Neurol. Centrlbl.*, **29**, 962–967.
MCFIE, J., PIERCY, F. J., and ZANGWILL, O. L. (1950) *Brain*, **73**, 167–190.
MARSHALL, J. (1951) *J. Neurol. Neurosurg. Psychiat.*, **14**, 187–204.
NEILSEN, J. M. (1936) Agnosia, Apraxia and Aphasia, Their Value in Cerebral Localization. Los Angeles (Los Angeles Neurol. Soc.).
—— (1937) *Arch. Neurol. Psychiat., Chicago*, **38**, 108–133.
—— (1940) *Bull. Los Angeles Neurol. Soc.*, **5**, 135–145.
OPPENHEIM, H. (1885) *Neurol. Centrlbl.*, **4**, 529–532.
PATERSON, A., and ZANGWILL, O. L. (1944) *Brain*, **67**, 331–358.
——, —— (1945) *Brain*, **68**, 188–212.
PIÉRON, H. (1929) Principles of Experimental Psychology. Trans. by J. B. Minor, New York (Harcourt Brace).
PINÉAS, H. (1926) *Verh. Gesellsch. Deutsch Nervenarzte*, **16**, in *Deutsche Z. Nervenheilk.*, **94**, 238–248.
—— (1931) *Z. ges. Neurol. Psychiat.*, **133**, 180–195.
POPPELREUTER, W. (1917) Die Psychischen Schadigungen durch Kopfschuss. Leipzig (Voss).
PÖTZL, O. (1928) Die Aphasia lehre vom Standpunkte der klinischen Psychiatrie. Leipzig.
ROTH, M. (1949) *Brain*, **72**, 89–111.
RUSSEL, C. K., and HORSLEY, V. (1906) *Brain*, **29**, 136–152.
RUSSELL, W. R. (1951) *Proc. Roy. Soc. Med.*, **44**, 341–343.
SCHILDER, P. (1935) The Image and Appearance of the Human Body. London (Kegan Paul).
SMITH, S., and HOLMES, G. (1916) *Brit. Med. J.* (i), 437–441.
WORTIS, S. B., BENDER, M. B., and TEUBER, H. L. (1948) *J. Nerv. Ment. Dis.*, **107**, 382–387.

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SOME ASPECTS OF HUMAN ORIENTATION IN SPACE

(i) Sensation and Movement

BY

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The problems of the individual's relationship to the universe and to himself have occupied the thoughts of men from the earliest periods of history, mainly in their religious and philosophical aspects. It is only within the past three centuries that these relationships have come under precise consideration as problems in psychology and physiology.

Of specially intense interest at the moment is the problem of the mind-brain relationship. Hypotheses on this subject have been propounded by philosophers, natural scientists and by others, all of whom have in common the negative qualification of unfamiliarity with the processes and the observable consequences of cerebral disease, in terms of which all these relationships may so directly be studied.

The neurologist holds a position of prime importance with regard to this question and should be able, from his special field of experience, to make a contribution of fundamental importance to it.

There is a considerable neurological literature upon forms of disorientation ensuing upon cerebral lesions, not descriptive only, but embodying much theoretical discussion. The subject, in its nature complex, has been unnecessarily complicated by the great number of neologisms employed and by the lack of a desirable precision and of general agreement in their use. In a word, the literature is forbidding.

It is therefore the purpose of this paper, as far as possible, to use this nomenclature as little as possible and to put forward:

(i) A definition of orientation.

(ii) A hypothesis regarding human orientation together with a description of relevant clinical material.

I. Definition and Significance of Orientation

Orientation in space is a term describing the faculty normally possessed by humans and certain other organisms which permits them to have at all times precise knowledge of their position in relation to the outside world as it is perceived by them. This faculty is not a specific or an isolated one, but is dependent upon a variety of psychological and

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physiological processes. In order to be correctly orientated a man must be aware of the position in space, from moment to moment, of the parts of his body in their relation one to another, as well as of their relation to the outside world as perceived by him; he must also recognize the relation of objects in the outside world to one another and to himself. This all-important faculty, which is essential for daily existence, depends upon the integration of all sensory stimuli arising from within and from outside the body (presuming the existence of an outside world). Some integrative activities occur at a subconscious level. From conscious or psychological appreciation of certain stimuli, in the form of sensations, is derived the process we call perception.

We do not here wish to draw a sharp distinction between mind and matter, that is, between the psychic "body-image" and the anatomical and physiological "body scheme." It is the purpose of this paper to discuss those aspects of orientation which we believe are dependent upon the form and function of the body. We regard the psychological processes as inseparable from form and function. We do not see any necessity for postulating exclusively psychological processes, or for relying upon the electro-encephalographic interpretation of physiological processes to substantiate our conclusions, which were reached as a result of clinical investigation. We shall not involve ourselves in the vast philosophical tangle of ideas related to perception and orientation, in regard to the "real" or the "imaginary" world, except to mention briefly relevant theories.

We shall use the word orientation here as applied to the concept of a dynamic process and dependent upon psycho-sensorimotor integrity. The word orient is derived from the Latin verb *orior*, I arise, referring to the rising of the sun in the east, and no doubt associated with the religious act of turning towards the east or orient. Orientation in the sense in which we are using it implies the ability of the individual to relate himself to a fixed point. This point may be part of his own body or it may be perceived by him in space outside his body. Human orientation depends upon the complete integration and harmonious balance of the sensorimotor system, and all the senses contribute towards its achievement. We suggest that it is a dynamic process, because it involves a succession of events. In order to maintain orientation in space, the human subject must maintain and adjust the position of his body in its normal relations. The "fixed point" is fixed for only a single moment in time. The sensory stimuli from within his own body and from the outside world are constantly changing, and so need to be integrated and perceived incessantly. Usually they demand a response in the form of movement. Orientation is not separable from movement and movement is inseparable from sensation. *Sensation is an essential, continuous precursor and accompaniment of movement* in either a positive or negative degree. The motor response, action or inhibition, is not separable from the sensory stimulus.

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Movement is sensation.

Of the sensations which contribute towards orientation, vision and "feeling" (a term used to describe the perception of touch, posture, and joint and muscle position change) are the most important. "Feeling" is possibly more valuable than vision, for it is certainly a greater handicap to lose unilateral posterior column sensation than a homonymous field of vision. The blind person is capable of a full life, of artistic production and tremendous skills, such as are possessed by certain blind organists. The advanced tabetic is completely paralysed and made helpless by his sensory defect. We may note the fact that transmitting fibres for the "feeling" modalities of touch, posture, and joint position change are grouped together anatomically and physiologically in a single group of nerve paths, the posterior columns. The remaining modality subserved by the posterior columns, vibration, is related developmentally to the eighth nerve system, originally a mechanism for the appreciation of vibration in the surrounding fluid, later becoming a specialized apparatus for hearing and certain aspects of balance.

It is usually taught that spatial orientation is a function of the minor hemisphere probably controlled by the parietal lobe. Certainly, patients who suffer from one aspect of disorientation, the inability to recognize familiar surroundings in the outside world and the inability to find their way in their surroundings, may have a lesion in this situation. These defects may perhaps be due to the inability to apprehend direction, that is, the movement of bodies in space, in specific directions. In this paper we are discussing orientation in its widest sense, as depending upon the entire sensorimotor system, and therefore we do consider it controlled by, or "represented" in, any one part of the nervous system. We wish at this point to state that while we believe that orientation with its physiological and psychological implications involves form, or "anatomy," we do not regard "representation" as necessarily more than an artificial segregation of function directly related to experimental procedure. Walther Riese (1950), in his book "The Principles of Neurology," says "Since the days of Jackson we use the term representation, but . . . what the representation of parts of the body or of movements really means, nobody knows." We do not, in fact, understand the implication of anatomical structure. For example, let us consider the anatomy and physiology of the visual pathways. We know that certain fibres leave retinal cells and remain on the same half of the mid-line, while others cross to the opposite side. Investigation has shown that there is a "point-to-point" representation of cells in the pathways, from the retina to the occipital cortex. The left hemisphere is mainly in charge of right-sided action as shown by the efferent crossing of motor paths from left to right and corresponding crossing from right to left of afferent fibres. This anatomical pattern therefore allows the whole of the right side of the body with its visual extension in the right homonymous fields to be

'represented" in the left cortex. While we recognize the convenience of such an arrangement, we have simply stated a fact concerning form and have come no nearer to the understanding of function. To quote Riese once more, "It is to the credit of human intelligence and creativeness to have conceived a doctrine as a mighty instrument for the discovery of natural phenomena, and yet borrowed the first principle of this doctrine not from facts, which we worship too much, but from a scheme or design of our own, which we underestimate too much."

Professor F. Wood Jones (in a personal communication) has told us that a "crossed" nervous system exists in all vertebrates. All degrees of crossing of nerve tracts may be seen, from the complete decussation of the visual pathways in a hare or bird to the partial decussation of the visual pathways in man. In man, few, if any, nervous pathways do not cross the mid-line to the opposite side of the body. Even the afferent cerebellar fibres, which do not cross on entering or at a higher level in the cord, relay with the cerebellar efferents which cross to the opposite red nucleus. Uncrossed pathways do, however, exist, such as the anterior corticospinal tracts, the functions of which have been little studied. It is possible that the crossing of nerve fibres is related to function. Glees and Cole (1951) note the variations in numbers of crossed and uncrossed fibres of the pyramidal tract in studies of degeneration of cells and suggest "that in motor acts which demand greater skill, the hemisphere which gives rise to a comparatively large proportion of crossed fibres has a slight advantage over the other." The crossing of nerve pathways directs attention to the "double" pattern of vertebrate structure. Hughlings Jackson (1874) said: " That the nervous system is double physically is evident enough. This is a very striking fact, but one so well known that we are in danger of ceasing to think of its significance—of ceasing to wonder at it." Vertebrates are arranged about a central longitudinal axis, the position of which is related to postural and action stress in response to gravity. This central axis forms a mid-line about which symmetrical structures are arranged, as the eyes, ears and limbs. Certain mid-line structures, such as the tongue and trunk, are formed by the union of two symmetrical halves. Unilateral organs, such as the liver and spleen, are derived from mid-line structures which have migrated to lateral positions.

In regard to the sensory apparatus in particular, there are *two* eyes, *two* ears, *two* hands. The central connexions of sensation are all in twos; two olfactory bulbs, with two sets of filaments from two places on the nose; two sets of taste fibres, for the anterior two-thirds and posterior one-third of the tongue. There are two brachial and lumbar plexuses, two spinothalamic (dorsal and ventral) tracts, posterior columns, fillets, thalami, and spino-cerebellar tracts. Similar examples of efferent apparatus are seen, for example, in the two sets of pyramidal and extra-pyramidal motor fibres, two sets of lower motor neurones to the muscles.

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We believe that this "double" pattern, anatomical and physiological, is directly related to the function of orientation and we shall later attempt to demonstrate this fact.

We wish now to consider the statement that orientation is dependent upon all the senses at once and is only in part or at times a conscious process. There is no orientation in terms of one sense alone. There is no practical sensation in any modality of itself until there is sufficient experience and memory for associated knowledge to be realized. Any one aspect of orientation is dependent upon all the others. Berkeley (1709) said:

> "What he sees only suggests to his understanding, that after having passed a certain distance, to be measured by the motion of his body, which is perceivable by touch, he shall come to perceive such and such tangible ideas which have been usually connected with such and such visible ideas. But that one might be deceived by these suggestions of sense, and that there is no necessary connexion between visible and tangible ideas suggested by them, we need go no further than the next looking-glass or picture to be convinced.
>
> "The ideas of space, outness and things placed at a distance, are not, strictly speaking, the object of sight; they are not otherwise perceived by the eye than the ear. Sitting in my study I hear a coach drive along the street; I look through the casement and see it; I walk out and enter into it; thus, common speech would incline one to think, I heard, saw, and touched the same thing; to wit, the coach. It is nevertheless certain, the ideas intromitted by each sense are widely different, and distinct from each other; but having been observed constantly to go together, they are spoken of as one and the same thing. By the variation of the noise I perceive the different distances of the coach and know it approaches before I look out. Thus by the ear I perceive distance, just after the same manner as I do by the eye."

In order to demonstrate the full implication of the clinical disorders later described, it is now necessary to mention briefly certain essential and at times obvious facts of human awareness and behaviour.

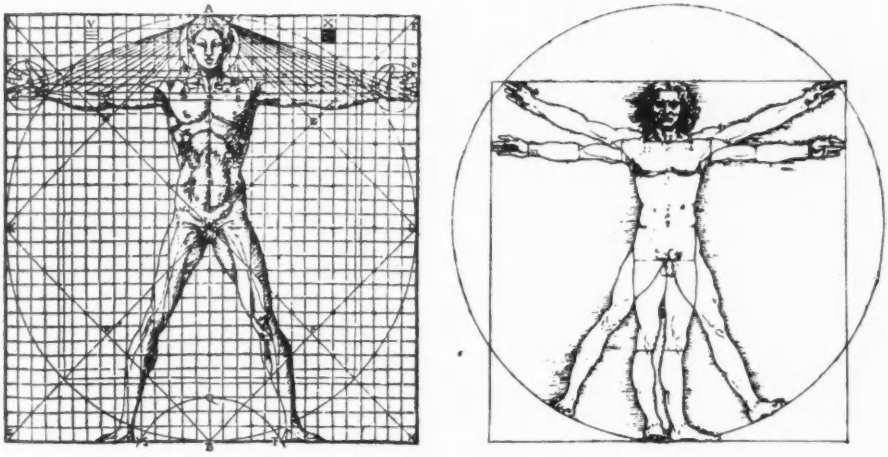
The normal person at an early age comes to recognize himself as an individual, distinct and separated by space from other individuals and objects, though recognizing others as similar to himself in many respects. He believes that he is surrounded by space and that his body occupies a certain volume of space, which is fixed at any one given moment in time. All his conceptions about space are derived from his personal relations: that is to say, he measures space relative to his body. His sensations about himself form his self-made yardstick for the outside world. He relates objects in space to the position of his body, considered as a whole and in separate parts, in a succession of moments of time. He is well aware of his height, less so of his breadth, and least of his thickness. He is aware of the polarity of his body in the longitudinal direction and also of the symmetrical disposition of his limbs on either side of the mid-line.

Such awareness calls forth description and the use of simple terms, such as "right, left, up, down, to, from, surface, mid-line, back, front, top,

bottom, halves," and so on. More complicated ideas are described in such words as "turned round," "back to front," "if I were you," "mirror images," "upside down" and even "inside out." These ideas are related to the individual's ability to project a mental image of himself into space. The term "projection" is used here to describe the mental process by means of which an individual is able to picture himself, or "imagine," his body, at a given moment in time as occupying a position in space with different body-environment relations from those immediately perceived by him at that moment.

The normal human being is able to move through his local space in any radial direction. (Certain animals such as dogs and horses have difficulty in going backwards and sideways, usually moving forwards or about the circumference of a circle.) He is also able to rotate about his vertical axis. He is able to rotate about his transverse axis less easily, and only as a rule with suitable support (as in performing somersaults and horizontal bar gymnastics), or about his front-to-back axis (as in turning cartwheels). Excessive performance of these latter unusual rotations will, in the untrained person, produce the disorientation of vertigo, but in the trained person familiar with the unusual sensations, they may be carried out without vertigo.

We behave as if we occupied the centre of a sphere, with separate or accessory spheres of action for contributory sensory and motor performance. Artists make use of this fact in figure drawing (fig. 1). The compound visual fields are roughly circular and allow a tubular, conic or beamlike extension of space. Taking the visual fields in conjunction with



a *b*

FIG. 1.—Figures from manuals of drawing (*a*) by Leonardo da Vinci; (*b*) by an unknown Renaissance artist.

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tactile range, which for each hand is roughly equal in the to-and-fro plane to the visual field in the vertical plane, we have two tubes at right angles to each other, and their volumes of overlap will be roughly spherical. The auditory field is a truncated sphere, with its centre at the head, its lower border, which is the ground, being flat.

The limb fields are roughly circular because the limbs consist of radial structures arranged about joints permitting varying degrees of rotation. We can move the arm in wide circles about the shoulder, and the leg less widely about the hip. The elbow and knee allow more limited circular movements, which can be performed in one plane only, no lateral mobility being possible.

Vision assists a person to extend himself forwards and laterally into his spatial environment, but only when integrated with associated ideas of touch and postural sense.

> "The judgment we make of the distance of an object viewed with both eyes, is entirely the result of experience. If we had not constantly found certain sensations arising from the various disposition of the eyes, attended with certain degrees of distances we should never make those sudden judgments of them, concerning the distance of objects; no more than we would pretend to judge of a man's thoughts by his pronouncing words we had never heard before."

The quotation is again from Berkeley (1709). As mentioned above, the individual also has the ability to project a mental image of himself in space, both within his field of vision and beyond it. This imaginary projection of his body may be performed in space previously experienced and remembered, so that a person can recall places and directions which he has known in the past, always in relation to himself. A further projection of both the person and his extension of himself into the world beyond may result in the conception of abstract or interstellar space.

This faculty of the human for mental projection of his image into space is an extremely important one. Many other faculties depend upon it and are related to it, as we shall later attempt to show.

We have also the ability to perceive objects in space in three dimensions simultaneously. We are aware of length, breadth, and depth of objects in a single impression. We are able to preserve our concept of three dimensions when perceiving only two dimensions of an object, this faculty being especially the result of past experience. We achieve, as we grow up, a pattern, a "Gestalt," of the three-dimensional character of objects, which we are able to apply to perceptions of a visual and tactile nature, and to complicated combinations of them, which is often labelled "experience," "habit," and "result of practice." For instance, those interested in aircraft or motor cars can often tell the type or make long before the details are clearly visible.

The anatomical and physiological details of orientation have been precisely described by Brain (1951) in a discussion of vertigo and disorientation. In his Textbook of Neurology he states:

"The maintenance of an appropriate position of the body in space depends in man upon several groups of afferent impulses, of which the following are the most important.

(1) From the retinæ are derived visual impulses which in contributing to our perception of visual space are intimately concerned in spatial orientation.

(2) Equally important are impulses derived from the proprioceptors of the ocular muscles. The degree of accommodation and ocular convergence required to produce a sharply focused image of an object upon the maculæ conveys information as to its distance from the eyes, and the state of contraction or relaxation of the external ocular muscles in conjugate ocular deviation contributes data to our recognition of "above," "below," "to the right of," and "to the left of."

(3) The labyrinth is a highly specialized spatial proprioceptor. The otoliths are mainly concerned in the orientation of the organism with reference to gravity, while the semicircular canals respond to movement and angular momentum.

(4) The proprioceptors of the joints and muscles of the neck are of importance in relating labyrinthine impulses which convey information solely concerning the position of the head, to the attitude of the rest of the body.

(5) The proprioceptors of the lower limbs and trunk are concerned with the position of the body in relation to the acts of sitting, standing and walking.

The afferents from these various sense-organs are mutually related by central mechanisms, of which the cerebellum, the vestibular nuclei, the posterior longitudinal bundle and the red nuclei are probably the most important, and which constitute reflex paths from which the position of the body is normally appropriately oriented. From these lower centres impulses reach the cerebral cortex mainly in the temporal and parietal lobes and so influence voluntary movement. Vertigo may result from the disordered function either of the sensory end-organs or of the afferent paths or of the central mechanisms concerned."

Paragraph 2 conforms strikingly with Berkeley's statement derived from abstract considerations alone, almost two hundred and fifty years ago. He said:

"This disposition or turn of the eyes is attended with a sensation, which seems to me to be that which in this case brings the *idea* of greater or lesser distance into the mind. Not that there is any natural or necessary connexion between the sensation we perceive by the turn of the eyes, and greater or lesser distance. But because the mind has by constant *experience* found the different sensations corresponding to the different dispositions of the eyes, to be attended each with a different degree of distance in the *object:* there has grown an habitual or customary connexion between those two sorts of *ideas*. So that the mind no sooner perceives the sensation arising from the different turn it gives the eyes, in order to bring the pupils nearer or further sunder, but it withal perceives the different idea of distance which was wont to be connected with that sensation."

We can see from these details the complex nature of orientation, and also the impossibility of localizing the faculty. Vertigo, itself a disorientation, signifies a condition of a person's altered relationships within himself or to his surroundings. A giddy person feels himself spinning, the floor rushes up to meet him, he becomes intensely confused and loses awareness of his position in space. It is true also to point out that clumsiness and "ataxia" are disorientations. The "useless limb" as described by Oppenheim, and occurring in disseminated sclerosis, is a disorientated part. So are phantom limbs and also the limb temporarily

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affected by "pins and needles." A knock on the "funny-bone" produces a form of disorientation. Disorientation may also be found quite normally in people learning new skills. "I am all thumbs today" says the pianist, or the knitter, or the mechanic.

II. Hypothesis

Orientation in the sense in which we are using it here implies the ability of the human individual to integrate all and perceive certain of the sensory impulses arising from his entire body and to relate—not necessarily at a conscious level—one set of sensory information to another. (Perception is here defined as the qualitative experience of a conscious individual, evoked by a series of events including the "unconscious" reception, selection, differentiation, integration and interpretation of sensory stimuli.) By this means a man is able to appreciate the form and position of his own body in relation to the outside world. He is able to judge direction and distance with reference to himself, and also the relative positions of objects in the outside world to one another. As a result of learning, he is able to apply conceptual terms to direction and position, and to orientate himself in an abstract or remembered environment not immediately perceived. In this paper we are mainly concerned with those aspects of orientation which depend primarily upon the *immediate* integration and perception of sensory stimuli. We postulate this theory, that the human individual being symmetrically arranged about a longitudinal axis from head to foot in common with all vertebrate animals, orientates himself in a manner directly related to this structure. The limbs and extremities of the human are in pairs of a similar structural pattern and are also arranged more or less symmetrically about central longitudinal axes. We suggest that all movements in space are likewise related to this structure, and are performed in directions both parallel to the central axes of the body, limb or extremity, and also in a rotatory manner about them. We have suggested that orientation involves movement in relation to a fixed point. The afferent stimuli upon which orientation depends are not static but flow ceaselessly from the body and the outside world throughout the life of an individual. The "fixed points" are therefore fixed only for a given moment in time. There is a constant need for adjustment so that the relationship of mobile parts to "fixed points" is preserved. We suggest that orientation within the body of the individual, as well as his ability to understand direction and position in the outside world, involves all these factors. We suggest that the mobile parts are the symmetrical halves of body, limb and extremity, and that these are maintained in a direct and constant relationship to fixed points on their central longitudinal axes.

Orientation and movement are thus dependent upon complex sensory patterns which must involve the entire nervous system of the organism, and a defect of a part involves disorientation of the whole.

Orientation and movement are inseparable. Both have their origin in sensation.

This hypothesis will be further developed and its clinical application demonstrated in the following pages.

III. Clinical Considerations

We shall now analyse in greater detail man's ability to orientate himself in relation to his structure. The afferent impulses derived from the entire body which assist the human to maintain his position in space and propel himself through space have been outlined above. The individual is aware of certain of these impulses; others do not reach consciousness. The human body is anatomically divided in two symmetrical halves on either side of the longitudinal axis. This axis is fixed and forms an imaginary central core in the mid-line of the body. In man, the central area includes the mouth, nose, and trunk, and these parts are phylogenetically the oldest. The eyes, ears and limbs belong to the symmetrical halves of the body. Movement in space may take place in the longitudinal direction of the axis—that is, parallel to the axis—and in a circular or rotatory manner around the axis. Gross movements or postures of the body such as standing upright, walking, turning, sitting or lying, involve both halves of the body, moving parallel to, or radially from, and rotating around, the central axis.

Movements may, of course, be confined to a whole limb or its extremity or even to a single digit. When smaller movements are performed, the central axis shifts, as it were, to the limb or to the extremity which is involved. The parts are still arranged more or less symmetrically about the long axis. The movements of supination and pronation are a simple example of rotatory movements around the central axis of the forearm. Similarly, movements of the hand are either parallel to the axis, as in making a fist, or combined with rotation, as in handling an object, writing, turning knobs and so on. We have to remember, of course, that the longitudinal axes of the parts are not necessarily parallel to or in the same planes as the longitudinal axis of the whole body.

Movements may be confined to the ipsilateral half-field of space or they may involve the crossing of a limb to the opposite field of space. Crossing is probably a more complicated performance than ipsilateral movement. We may conclude that man explores space in a radial manner from central points in space which vary in their positions along longitudinal axes throughout the body. His perception of the three-dimensional nature of objects is partly due to this function. It is difficult to gain information regarding height, breadth, and thickness in a single impression by movements in directions purely vertical or horizontal. Rotatory movement of the fingers greatly assist the perception of the surface planes of objects.

The longitudinal axis or mid-line of the body has important psychological implications as has been demonstrated by Pick (1922), Rosenberg

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(1912), Herrmann (1924) and Schilder (1935). It was stated above that the individual is able to projeet a mental image of himself, by means of abstract thought-processes, into space. It was also said that in any individual, all ideas concerned with surroundings, space, and objects in space, are related to the individual himself. We believe that the image of the body which is projected in space is of the same pattern as the immediately perceived body—that is, it is formed by two symmetrical halves linked along a central axis. Space itself, especially in a sighted individual, is also regarded as consisting of two lateral fields which fuse at their medial borders. In the very young (and in certain patients suffering from disease of the nervous system) this mental projection of the body is performed directly forwards, the right side of the body into the right field of space, the left half into the left field of space. The young child later learns to rotate his projected image of himself and his movements so that he is able to imagine himself facing himself. He then becomes aware that the right side of an individual who faces him is opposite to his left side and vice versa. This ability to rotate a projected image in space has an important bearing on such functions as reading, writing, recognition of directions and skilled movements. "Dressing apraxia," for example, may be considered a disorder of the function. We shall discuss these points in detail later.

The names "right" and "left" as applied to the two halves of the body and to space are concepts learned, often imperfectly, during development in childhood. It is possible for a patient to lose the understanding of the concept of "right-sidedness" and "left-sidedness," although he remains aware that he possesses two halves of his body on either side of the mid-line. Similarly, he may lose the understanding of such terms as "nearest and farthest," "North," "South," "East" and "West," "above and below," and other topographical concepts.

An individual becomes disorientated (i) when the integration between the two halves of his body is disturbed, and especially when he is deprived of the power of contrasting one against the other; (ii) when he loses the ability to perceive sensory impulses arising from one half or part of his body, and as a result is also unable to perform parallel or rotatory movements with, or in relation to, that part (as may occur with any lesion of the peripheral or central sensory nervous system); (iii) when he loses the ability to project or rotate the abstract image of his own body in space.

These conclusions are based upon the study of a number of patients (some of whom will be described in this paper) suffering from various forms of disorientation. It will be seen that these patients had:

(i) Imperception of one half of the body, or lack of awareness of one side or part of the body.

(ii) Confusion between one side of the body and the other. Two of the

patients described had difficulty with the identification of their own limbs, confusing them with the bodies of others.

(iii) Impaired appreciation of sensation from one part or half of the body resulting in a "sensory paralysis" of that part—that is, difficulty with voluntary movement, writing, construction and so on.

(iv) Difficulty with extension of the spatial environment due to visual defects.

(v) Difficulty with the projection of the mental image of the body into space or difficulty in the control of the projected image.

(vi) Inability to make movements which involved crossing the mid-line of the body with one limb to the opposite field of space.

(vii) Inability to perceive the three-dimensional nature of objects or to construct three-dimensional patterns.

(viii) Difficulty with rotation and direction of movements, resulting in "mirror" performances.

There is an extensive literature describing clinical disturbances similar to those listed above. It is too large for critical review at this place, and has been fully quoted by others.

Books and papers in current use generally employ terms such as "agnosia," "apraxia," "dysgraphia," "reflexive apraxia" and so on. We have been careful to avoid the use of such terms, and have quoted only certain relevant cases in connexion with similar cases of our own. We have avoided these terms because we believe that they are too often used (i) to summarize a set of clinical impressions, instead of describing them; (ii) to suggest a specific defect with well-localized pathological processes; (iii) to imply isolated faculties of behaviour. Thus, we find under the heading "aphasia" the term "expressive dysgraphia," under the heading "apraxia," "ideomotor dyspraxia," and under the heading "agnosia," "visual object-agnosia" to describe a patient's difficulty in writing, and reading after brain damage. No doubt, some authorities will object to this criticism, saying that these terms have a precise meaning, if properly understood. We contend that formal submission to ever-varying definitions of behaviour patterns prevents us from enlarging our knowledge of the underlying mechanisms of behaviour.

Case 1.—C. B. (seen at University College Hospital, London, W.C.1, while under the care of Dr. E. A. Blake Pritchard).

This patient, a right-handed nursing sister, of 44 years, was admitted to hospital because, she said, she had been "falling about a great deal," and the doctors for whom she worked "had insisted on an investigation." She herself did not believe she had any serious illness. Her falls occurred quite suddenly, always to the left side, and were not accompanied by any disturbance of consciousness. On one occasion, the patient fell so heavily that she fractured some ribs on the left side. On another occasion, she injured her head. She could in no way account for her falls. She had also recently noticed that she had a tendency to bump into objects

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on the left side. She had, however, been at work until a few days before entering hospital.

On examination she was found to be suffering from a variety of defects. *A total defect was present in the left homonymous field of vision* which reached almost to the mid-line. In the remaining portion of the field, visual inattention could be demonstrated. Consensual deviation of the eyes upwards and to the left could not be performed. The patient could turn her eyes to the right and downwards. The patient was unable to protrude her tongue on command, nor could she open her mouth wide, nor show her teeth properly. She also had difficulty when asked to frown. Involuntary movements were not impaired. These difficulties suggested an "*apraxia of the face*." The left side of the body was affected by what may be termed a sensory paralysis. The patient was unable to initiate or perform voluntary movements with any accuracy or precision, on account of a gross loss of postural sense, though no disturbance of upper and lower motor neurone and cerebellar function was demonstrable by the traditional tests. A hypæsthesia (pin-prick) was also present in the left half of the body (with marked tactile inattention in the left arm and hand). She was unable to identify objects with the left hand and had defective two-point discrimination. In addition to the left hemianopic field defect, the patient had another difficulty with vision. She complained that when she tried to read, the words "shunted." She said that she would read a sentence beginning at the left-hand side of the page, and when she reached about half-way across the page "the words on the right half of the page seemed to move across from right to left towards the mid-line"—this "shunting" made the patient feel sick so that she could not continue to read. She suffered at times from attacks of very severe headaches—described as pain in the right occipito-parietal region. The pain was violent, came on suddenly and lasted from a few minutes to several hours. While the pain was present the patient felt sick and vomited at times and had even greater difficulty with vision. She complained on one occasion that "when the pain comes on the whole room whirls madly and I feel blinded." She had to lie on her back with her head sharply retracted while the pain was present. At the onset of pain, her face took on an expression of acute apprehension. Asked why she lay in the particular position which she adopted, she said that if she sat up "everything is complete chaos. Everything swings, and me with it. It makes you feel so nauseated, doesn't it?"

Between attacks of pain, she seemed comfortable but apathetic. She was slow to respond to questions, and suffered from an impairment of memory so severe as to be reminiscent of a "Korsakov" defect but without confabulation.

The patient was co-operative and pleasant except when she had a headache. She made no spontaneous complaints, but when questioned about her state, she would say that her left side felt "queer," or "odd," or "clumsy" . . . "I can't hold on to things . . . I can't get hold of them . . . I can't move up my leg." She was quite unaware of the position in space of her left hand, but on being directly questioned about it, she said she could think of and imagine this hand. (She was perfectly orientated regarding right and left.) While her left hand was being discussed she looked at it, and raised her left arm in an experimental fashion saying "That's a queer thing, I don't feel as if I'd got it there." When objects were put into the left hand during the test for identification, the patient said that her left hand felt heavy and larger than the right, "But it's not larger when you look at it," and that objects "didn't feel the same" in the left hand as they did in the right. "It's like having a sponge or something thick over the fingers." The patient was distressed because she could not cut or file her finger nails. She tried to do this on many occasions, but found it impossible with either hand. She was, however, able to clean the nails of the left hand with her right, but not vice versa.

She was carefully examined at brief intervals for some time. For some days her

condition appeared to deteriorate. During this part of her illness she showed some extremely interesting defects of orientation. These will now be described in detail.

The patient appeared to have some difficulty with crossing from one-half of her personal space to the other: that is, difficulty in voluntary movement across the mid-line of her body. This difficulty was first noticed when she was asked to draw a daisy head. She took the pencil in her right hand and drew a circle. She then began to draw the petals on the right half side of the circle, moving in a clockwise direction. When she reached the mid-point of the lower margin of the circle (i.e. at about "6 o'clock") she changed the pencil from the right to the left hand and completed the drawing. She was asked not to change hands but to complete the drawing with the right hand. This she found quite impossible to do. The test was performed on numerous occasions. She was never able to cross the mid-line of the circle with either hand.

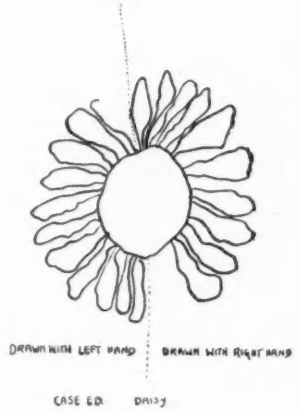

FIG. 2.

When she was forcibly restrained from changing the pencil to the opposite hand she continued to draw petals on the ipsilateral side of the circle instead of proceeding around the periphery. An example is shown here.

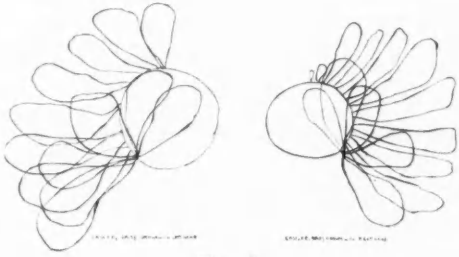

FIG. 3.

This curious difficulty was exhibited in various other drawings and actions. When asked to move a coin across a piece of paper from one side of the page to the other,

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the patient moved the coin as far as the mid-line of her body with the ipsilateral hand and completed the action with the opposite hand. This happened both when the patient's eyes were open and when she was made to keep them shut. In addition to the above difficulties, the patient had a defective knowledge of the mid-line of her own body. When asked to touch the middle of her forehead between her eyebrows she always misjudged the point by several inches with either hand. Similarly when her eyes were closed she was unable to touch her umbilicus with either hand. The point she touched was always to the right of the mid-line with the right hand, and the left of it with the left hand.

When objects were placed in the patient's left hand, she made strenuous and seemingly compulsive movements to take them with the right hand. During the test for identification of objects in the left hand, the patient's right hand had to be forcibly restrained.

When an object was held in front of her and she was asked to take hold of it, the patient generally raised and used both hands to take it. Having once grasped it in both hands she seemed to have some difficulty in transferring it to one or other hand. The patient described this action as follows: "Things seem lost when I go to get hold of them with this hand" (indicating the left hand) "until this one comes and helps it." Asked why she should try and take objects with the left hand she said she "felt a tremendous desire to do so." As soon as she touched the object with her left hand the right hand came up automatically and forcibly. When the patient was asked to perform certain movements with the left hand and arm she showed gross apraxia.

On another occasion the patient described her actions as follows: "There's a horrible urgency to use the left hand but when I try to use it the right hand comes too. The left hand doesn't know what to do but it wants to."

The patient was unable to hold her arms across her body even when shown how this action should be performed.

She also had some difficulty with the rotation of objects. She was given a stick which was placed before her so that it lay in a horizontal manner. One end, at the right hand side of the patient, was marked with a cross. She was asked to move or rotate the stick in a clockwise or anticlockwise direction, so that the marked end lay on her left-hand side. She puzzled over this problem for a long time, making small ineffectual movements with the stick, but she was unable to rotate it any distance at all.

Vision.—When the patient was first admitted, she was able to read for a limited time, and could understand what she was reading. After a while the "shunting" described above grew worse and the letters and words seemed to be shifting constantly from each side of the page towards the mid-line. The sense of their moving was accompanied by nausea. One day, however, the patient was found reading the newspaper upside down and from right to left. She was vaguely aware that something was wrong. She said that following a severe headache the previous day "things suddenly seem to swing upside down. They may right themselves again or they may remain upside down. It feels as if my eyes get loose." Reading was fairly well performed when the page was held upside down, even though the patient was not sure if the paper was in the normal position or not. She thought that the upside-down position was correct. The letters continued to "move all the time." The patient was quiet, rather confused and apathetic during the interview. The inverted vision persisted at time for several days. She was partially aware of the strangeness of her behaviour and became suspicious and somewhat unco-operative when asked to read. She was once handed a newspaper upside down and asked to put it in the correct position for reading. She said "It's the right way up as it is," and suddenly asked "Is it your right way up or mine?"

During this time her vision became increasingly impaired. She suffered from

gross visual disorientation the nature of which is too complicated to be described in this present paper, and lost her sense of stereoscopic vision. She finally gave up all attempts at reading and tried not to use her eyes at all. She continued to have attacks of inverted vision, and described her difficulties when trying to eat a boiled egg; "I just couldn't eat it—it kept on being upside down." On one occasion she was found lying with closed eyes and on being asked what was the matter, she said she couldn't bear to see people "walking about on their heads—it looks *most* peculiar but their trousers and skirt edges remain perfectly straight when they really should fall downwards."

The patient generally lay almost flat on her back; she did this to avoid nausea. She said "I have to get my head straight and on a level with my body even if my eyes are closed. You know it's like those kaleidoscopes. Things whirl about. If there's more than one person I have to shut my eyes—they run together. It's terribly confusing. It makes me think of that French painter—Picasso. Perhaps he sees things like that . . ."

Sensation.—At the admission to hospital, the patient showed marked tactile inattention on the left. When stimulated on right and left sides simultaneously, she stated she felt the stimulus on the right side only. When stimulated on the left side alone, she was able to perceive the stimulus but localized it inaccurately. After some days, perception of tactile sensation and pin-prick on the left side of the body diminished. The patient then began to show alloæsthesia. When stimulated on the right side and asked to localize the stimulus, she pointed to a precisely similar position on the left side of the body, e.g. if touched on the right wrist, she localized the sensation as arising from the left wrist. This alloæsthesia could be demonstrated on the face, trunk and limbs. It was variable but became for a while almost constant. At times a stimulus on the left side of the body was located on the right side. At this time, the patient was asked to close her eyes and both her hands were placed palm upwards on the bed. An object was put in her *right* hand. She was asked to close her fingers over it. She closed the fingers of both hands. She was asked (her eyes were still shut) which hand contained the object. She said promptly "the left," but then, after moving each hand experimentally she changed her answer to "right." Shortly after this, when an object was placed in the right hand while her eyes were closed and she was asked to raise the hand which held it, she raised the left hand. When asked to open her eyes and see the object she appeared astonished that it was in her right hand—saying it "felt like the left." She was always able to name her right or left hand correctly when she was allowed to look at them. When the examiner stood on her right side and she was asked which side this was, she first inspected her hands carefully, compared them with the position of the examiner and then said "she supposed it must be the right." At this time her visual disorientation became very marked and she had difficulty in knowing the relative position of her feet and head, while her eyes were closed. She would at times point to her head when asked to point towards her feet while she was lying flat on her back, and vice versa. Again, when objects were placed vertically in her right hand while her eyes were kept closed and she was asked which portion of the object pointed up towards the ceiling, which down to the floor, she at times answered incorrectly, although feeling the object carefully. A cigarette lighter, a pencil and a nail-file were used for this test. This disorientation was inconstant. The patient was not aware of her mistakes but she did realize that her body and her world were a source of confusion to her.

Writing, drawing and construction.—In the early part of her illness, the patient was able to write normally, although very slowly. An example of her writing is shown here:

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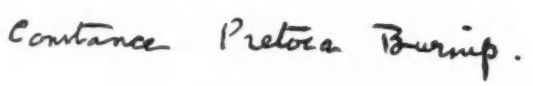
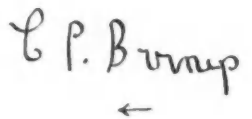


FIG. 4.

Soon after her admission to hospital, however, she experienced marked difficulty in writing, and seemed confused and hesitant. It was then discovered she was beginning to write (with the right hand), from right to left across the page—as shown here:



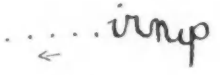


FIG. 5.

She became more and more confused, although at times still able to write in the correct manner. At such a time she was asked to write with her right and left hands simultaneously. The result is as follows:

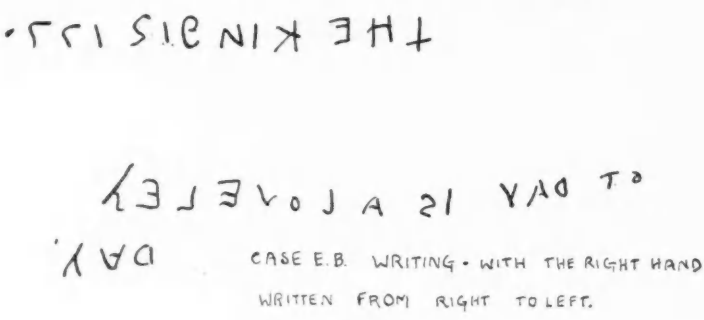
FIG. 6.

It should be noted that she did not write "mirror fashion" with the left hand, as is usually the case in "hysteria." She then began to write from the right-hand side of the page to the left, sometimes in mirror fashion, and sometimes mirror wise, and upside down, with the right hand. Examples are shown here:

The patient was aware that she was confused but had no means of judging whether her writing was correct or not. She was asked to copy certain designs, draw a clock, a picture of a man, and to copy designs from memory.

Examples of her performance are shown here:

The "mirror" reversal was also seen when the patient was asked to copy three dimensional constructed patterns, and stick patterns. The reversal was not entirely constant, as is shown by this example of her performance when copying stick patterns:



CASE E.B. WRITING · WITH THE RIGHT HAND WRITTEN FROM RIGHT TO LEFT.

FIG. 7.

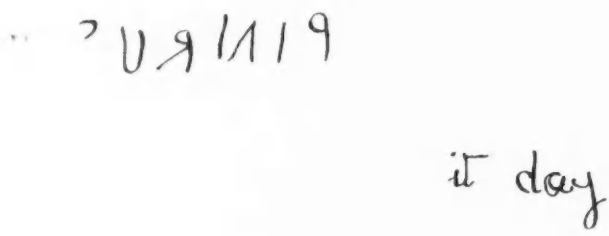
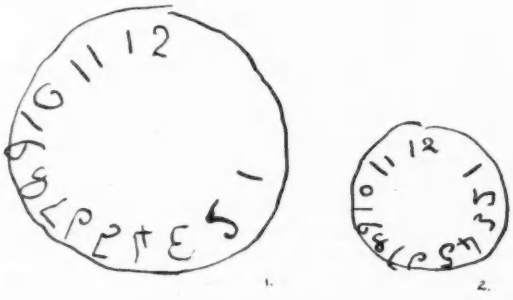


FIG. 8.



CASE E.B. DRAWINGS OF CLOCKS

FIG. 9.

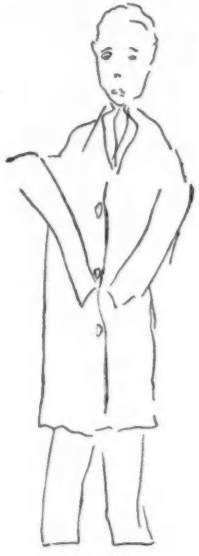


FIG. 10.

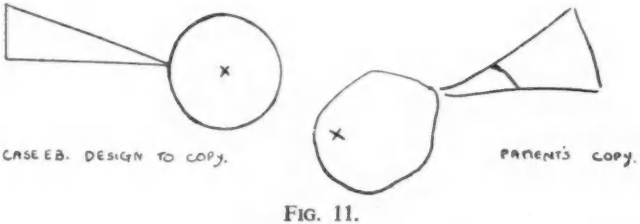


FIG. 11.

The first pattern was placed on the patient's left side and the copy was made to the right of the pattern. The second and third patterns were placed to the right and copies on the left. The confusion persisted until her vision had deteriorated to such an extent she was not able to carry out the tests.

Speech.—The patient demonstrated to a mild degree "backward" speech. She was at times slightly hesitant when talking and complained she was stuttering. She said that before using a word she had an impulse to spell it backwards—although when she said it "it came out all right." Very occasionally she pronounced a word backwards, especially during the testing for name objects, e.g. soap was called paos, and when she was asked to name an ash-tray, she hesitated for a long time before giving the word and said "Now I couldn't have said that without the other bit attached [meaning the second half of the word]—I couldn't have got it out."

The patient was asked to recite the alphabet aloud at a rapid rate. She did so, beginning at Z, and going backwards with great accuracy. It is doubtful whether a normal person performs this feat without training. Such training the patient denied. When asked to spell words aloud, the patient spelt them backwards, again more quickly and accurately, it was judged, than is possible normally.

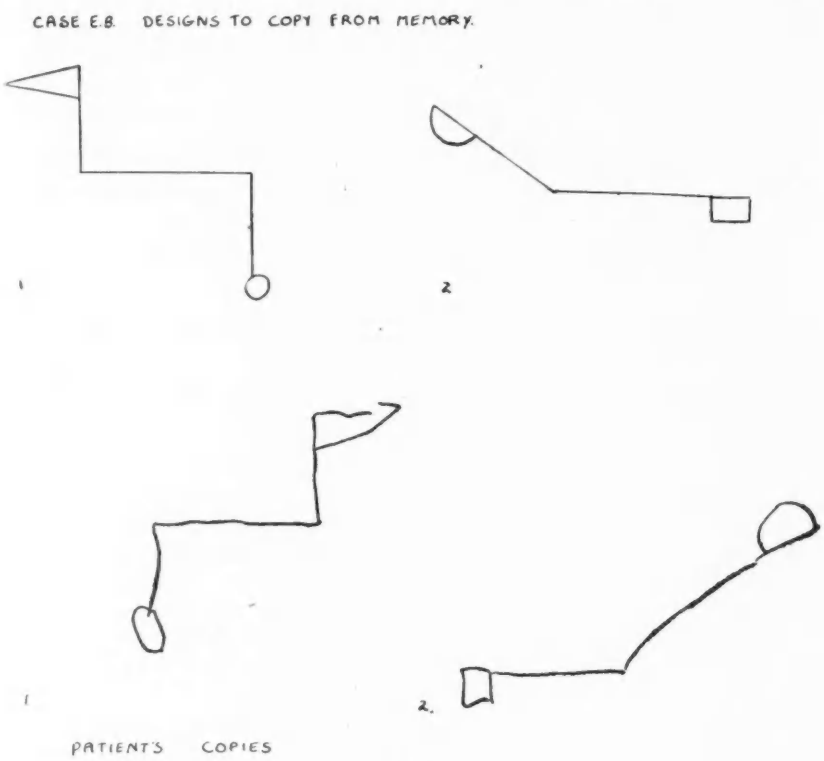


FIG. 12.

On one occasion she was asked for the name of her sister's dog. She said "Peke" after much hesitation, but added "e..k..e..p ... I keep on doing that—it's a good job I don't hear the radio backwards."

Hearing.—When the patient's vision was grossly deteriorated and she was having difficulty with the orientation of the two sides of the body, it became noticeable that she was localizing sound on the opposite side of the body to its origin. On being greeted by the examiner the patient looked searchingly for the source of the voice on the opposite side of the bed to which the examiner was standing. On being shown where the examiner was in fact placed, the patient seemed bewildered, and said "Oh dear, I'm upside down. I've noticed that sound seems to come from the opposite direction. The telephone sounds like that. It seems to come from there (points to the left) but I know it's there (points to the right). Sound is an awful muddle." She added "I hope they don't move me because I know some fixed points round me. I know Mrs. S. is on the *right* side of me and Mrs. M. on the *left*."

This "reversal" of sound persisted for a while. On a subsequent occasion during an interview, there was a banging and clattering noise outside the window which was directly opposite the door. The patient looked at the door said "Some one wants to come in." The patient was sometimes aware of her difficulty as described

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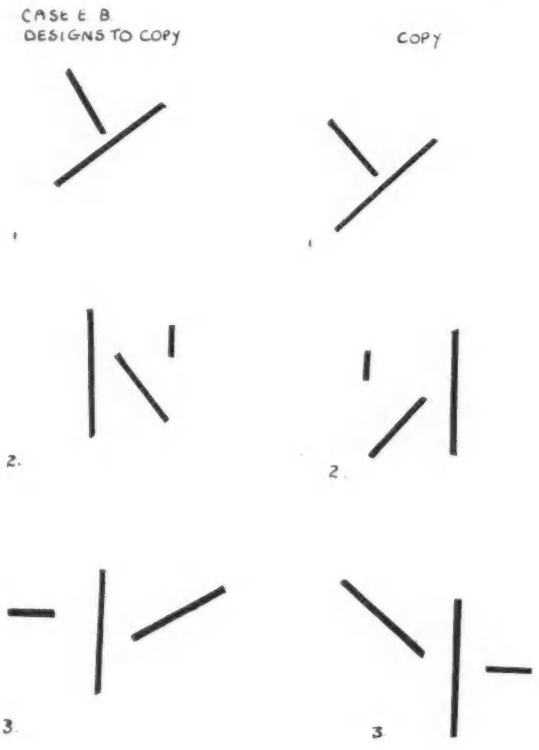

FIG. 13.

above. She said, "I expect things to be on the opposite side—I keep looking on the wrong side for voices. The person's not there."

At the time of writing this patient has been transferred to another hospital. She is still alive and reported to be making slow progress towards recovery. Towards the end of the period during which we saw her, she began to suffer from short attacks of "pins and needles" in the left leg and foot, especially while the headache was present. There was a suggestion that the left plantar response was extensor. When the patient was placed in a chair, she sagged over to the left side and felt "horribly sick." Her vision was still grossly disorientated.

The diagnosis of her condition remains uncertain.

Lumbar puncture revealed excess of cells and 200 mg. per cent of protein.

Ventriculography gave no clear indication of the site of any lesion. Hysteria was suggested. The authors believe, however, in the existence of organic disease, though they are uncertain of the pathology.

DISCUSSION

Case 1.—E. B. Similar cases have been described by Pick (1922), Rosenberg (1912), Herrmann (1924) and others. Akelaitis (1942)

describes a very similar state in a patient following partial section of the corpus callosum for the treatment of epilepsy (his Case 15). A patient of Trescher and Ford (1937) showed marked disorientation after the corpus callosum had been incised to remove a colloid cyst of the third ventricle. Cramer (1936) has described the "peculiar ataxia" which occurs with lesions of the corpus callosum and he quotes the case of a patient who suffered from a similar condition for eight years before death. Schilder (1935) discusses the mid-line in relation to the body image and describes also patients who are unable to "transfer from one side of the body to the other." Schilder also mentions patients who cannot choose the right or left arm to command in spite of the fact they know perfectly well which is the left and which the right side of their body. "Often they act with both limbs simultaneously when asked to move either the right or left side. They also make so-called associated movements." Schilder believes, however, that outside space and the body space differ in their structure. He admits, however, that "we do not know of cases in which the use of objects is disturbed while the use of the knowledge of one's own body is preserved." "Alloæsthesia," with the stimuli referred from the normal half of the body to the affected half, has been described by various authors, including Schilder (1935), and Hammond (1881). Patients who referred stimuli from the affected side to the normal one have also been described (Kramer, 1915; 1917). Mirror writing has been described at length by Critchley (1928). He mentions mainly right-handed patients who wrote "mirror-wise" with the left hand, and under these circumstances, the performance is regarded as a dissociation phenomenon and therefore hysterical. Mirror writing performed with the right hand in right-handed person should be regarded as a disorientation. (Critchley: personal communication.) Critchley also describes inverted writing and backward speech.

Case 2.—R. R. (N.H. No. 34717.)

This patient, a right-handed woman of 40 years, a former district nurse, was admitted to the National Hospital, Queen Square, under the care of one of us (W. G.). The following history was obtained.

About fourteen months before admission, she had struck her head forcibly against the door of her car and shortly afterwards became drowsy and complained of severe headache and neck stiffness. She was admitted to the local hospital, and a lumbar puncture was performed. A heavily blood-stained fluid was removed. There was xanthochromic staining of the supernatant fluid and a protein content of 200 mg.%. A diagnosis of subarachnoid hæmorrhage was made. The patient remained in the hospital for several weeks. On discharge she still suffered from headaches and loss of memory. She was at home under the care of her doctor for a year. She then attended the out-patient department of St. Richard's Hospital, Chichester, and was referred to the National Hospital.

On examination, the patient appeared very apathetic and unco-operative. When she was questioned regarding her history she was very vague and said "the past was very hazy. It all seems a very long time." She could not say exactly when her accident had occurred. When asked for her complaints, she said she had been worried

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by poor memory—and she had no other troubles. She burst suddenly into tears, without seeming very distressed. The weeping lasted a few seconds only and her mood then returned to the previous apathy. The patient said that, recently, sudden attacks of crying came on for no apparent reason, often when she was alone, and lasted a few minutes. During her stay in hospital she had several such attacks.

On examination she was found to be suffering from a left-sided field defect which was difficult to define precisely because of the patient's wandering attention and slow responses, but which was probably a left complete homonymous hemianopia. She seemed unable to protrude her tongue on command, and when asked to shut her eyes, did so momentarily only. There was a marked sensory defect on the left side of the body, including gross loss of sense of posture and position, with cutaneous hypæsthesia. There was an extreme neglect of the left side of the body and the left half of space. When her attention was directed to the left side of her body and she was cross-questioned regarding its usefulness, the patient admitted only that "her left arm felt queer." The reflexes were slightly increased on the left side. The plantar responses were flexor.

The patient suffered from a gross defect of remote memory. She had no idea of the time of day or of the passage of time. Although she had been a district nurse in Sussex, she was quite unable to give the names of any villages or towns in that county except the one in which she lived. She also showed a severe impairment of immediate recall. She replied very slowly to questions, complaining that she could not concentrate, and that "her head was muddled." She suffered from very severe headaches, mainly left frontal or right occipital in position. While the headache was present, and also at other times, she complained of nausea and occasionally vomited. In addition to these disorders, she suffered from disturbances of orientation now to be described in detail.

Sensation.—The patient neglected the left side of the body, as has been mentioned above. She kept the left hand under the bedclothes and used her right hand only, for eating, washing and all voluntary movements. She was asked to touch her nose with her right hand. She did this correctly. She was asked to repeat the movement with the other hand. She used the right hand again. "No, please use the *other* hand." The patient looked blank, said "Oh," thought for a moment and then slowly and clumsily performed the movement with the left hand. She was next asked to touch the left eye. She repeatedly touched the right eye. She was not confused, however, as regards the understanding of right and left sides. She could demonstrate quite correctly which side was which on her own body. However, when the examiner faced her, and she was asked to name the examiner's right or left hands, she did so incorrectly. She called the hand which was directly opposite her own right hand the examiner's right, and the one opposite her left hand, the examiner's left. When the examiner turned sideways to the patient, and she was asked to name the right and left hands, she was able to do so correctly.

Sensation was much diminished on the left, but this was thought to be partly due to the patient's inattention. When a pencil was placed in the patient's left hand while her eyes were closed, and she was asked to name what she held, she said she could feel nothing. She was asked to open her eyes and look at the object. She did so, laughed rather ashamedly and said she still could not feel it. She complained at times of sensations of "pins and needles" in the left hand.

On one occasion she mistook the examiner's arm for her own. While he held her left hand she was asked to show which was her left arm. She touched his arm and said "It must be this, I suppose."

Vision.—On her admission to hospital, the patient suffered from a left hemianopic field defect. Her vision slowly deteriorated and in addition to the field defect she suffered from visual disorientation. She complained that

when she looked at objects they seemed to move. When she tried to read, the "letters all ran together, towards the middle of the page." She also lost her sense of stereoscopic vision and suffered from other defects too complicated to be described here. She became unable to recognize objects unless she could handle them. When shown objects she looked at them and said she "can't focus properly—it all runs into one." When allowed to touch objects with her right hand she was able to identify them correctly.

Reading, writing and construction.—When she was admitted, the patient was able to read but neglected or could not see the left half of the page, e.g. when reading aloud:

The King of China's daughter
the patient read
"of China's daughter," missing out the words "The King."

Later her vision deteriorated and became confused. She was shown a newspaper the correct way. She said "That's upside down, isn't it?" and proceeded to turn it the wrong way up. She tried to read it thus, but complained of feeling sick and a pain in the head and gave up the attempt.

She was asked to write her name. She wrote "Rogers." She was asked "What about your first name?" She replied "What first name?" "What does your husband call you?" The patient said "Oh . . ." and wrote "Rosy" in front of the word "Rogers." At a later date she wrote her name as is shown here, together with the words "man" and "baby" which she was asked to write:

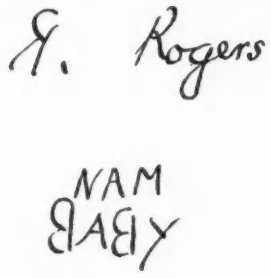

FIG. 14.

She was asked to copy certain designs, and to draw a clock and a daisy. Examples are shown here. The daisy demonstrates her neglect of the left side. The other figures show a "mirror" disorientation.

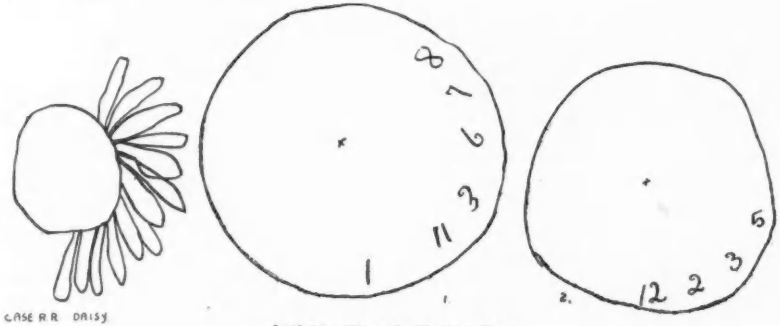

FIG. 15.

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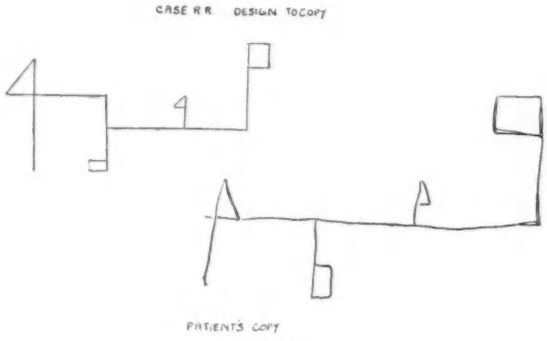

FIG. 16.

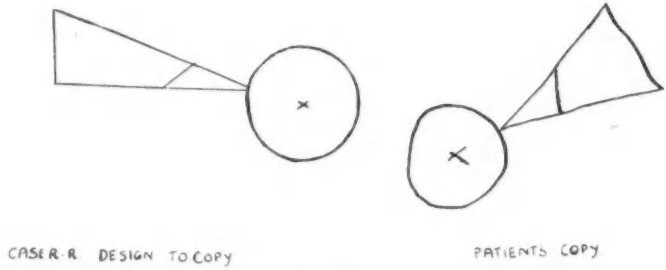

FIG. 17.

When doing the stick test this type of mirror reversal was again demonstrated, as is shown here.

This patient also failed to carry out the rotation of objects in a clockwise or anti-clockwise manner, as described in the previous case.

The patient's condition deteriorated slowly. She became more and more apathetic and exhibited a curious form of dementia. She seemed to lose her own identity. She was asked to write her name. She paused for a long time. She was then asked to write "Rogers." She said "That's not my name . . . my name is Burge . . . That's my father's name—my father was Commissioner for the Forest of Dean . . ." Questioner: "Who is Rogers then?"—after a long time the patient said: "That's my name, too." The patient was asked to write the name Burge. She could not do so. She could, however, spell the word aloud.

A letter was brought to the patient. She looked at it for a moment and said "It isn't for me." (At this time her vision was very defective.) She was told it was for her. She looked at it for a long time but seemed unable to open it. She insisted the letter was for one of the other patients.

She had always by the bedside two photographs, one of her husband and one of her son. When first admitted she was constantly showing the pictures to the examiner and saying how good and lovable these relations were. At this later date, however, she was shown the photograph of her son and asked his name. She said she didn't know. She took the photograph in her hand and inspected it for some time. She then said "That's one of my babies when I was a Queen's nurse." The examiner insistently demanded the name of the boy in the photograph. The patient said

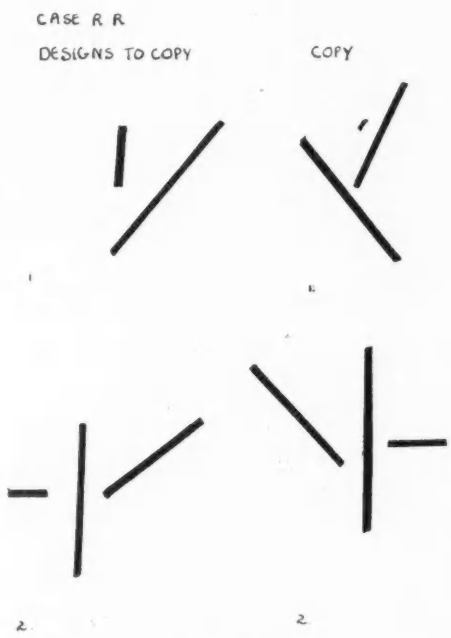

FIG. 18.

"He goes to Christ's Hospital School." Question: "Is he your own baby or someone else's baby?" The patient finally admitted, although apparently reluctantly, that this was indeed her own son. When shown the photograph of her husband and asked who this was, she took the picture in her hand and said "It wants cleaning, doesn't it?" Question: "Who is it?" A long pause followed. Question: "Is it your husband?" Answer: "It may be."

While the patient's vision was certainly poor at this stage and her memory grossly defective, the shape and frames of the photographs might have been sufficiently familiar for her to identify them.

The patient was shown her own face in a mirror and asked whose it was. She replied she did not know. Asked "Is it you?" She replied "No, I had long hair . . ." (This was after her head had been shaved for ventriculography.)

The patient was also examined by Dr. Macdonald Critchley who thought she suffered from an organic syndrome, possibly caused by biparietal lesions or cortical atrophy.

This patient is also still alive at the time of writing. While she was in hospital, arteriograms and ventriculography were performed but failed to reveal the nature of her lesion.

DISCUSSION

Patients who have difficulty with regard to the knowledge of the parts of their own bodies and inability to touch parts of their bodies when asked to do so have been frequently described. Liepmann (1920) has called such disturbances "reflexive apraxia."

XUM

Case 3 (N.H. No. 35202).

This patient, a man aged 60, formerly a clerical worker, was admitted to the National Hospital under the care of Dr. Purdon Martin, one day after he had collapsed suddenly in his home, falling unconscious to the floor. When he recovered consciousness, he was unable to see, complained of a severe left frontal headache and stiffness of his neck. On examination when first admitted, the patient was found to be suffering from a right homonymous hemianopia and slight weakness of right external ocular deviation. The patient was not dysphasic and was able to write his name. He was extremely confused as regards which side of his body was left and which was right, to such an extent that, according to the notes, "there was almost a right-left substitution." No "finger agnosia" was present, but his powers of calculation were defective. The patient realized he was confused as regards the right and left sides of his body, but the confusion cleared after some days. The tendon reflexes were present and equal on admission, and the plantar responses were flexor. No sensory abnormality could be detected. The patient continued to have certain difficulties, however. He complained he could not read—saying he thought he was "cross eyed sort of business." His two eyes, he said, didn't seem to focus as they used to—although the print was not blurred. It was rather that words seemed to get close together and get on top of each other. Also objects he looked at moved and got on "top of one another." The patient kept complaining he "seemed to see crossed." Not only did this patient "see crossed" but he wrote and drew and thought in a manner suggesting a "mirror" disorientation. Some days after his admission he was quite clear as regards which was his right side and which his left. When asked to indicate the examiner's right and left hand (while the examiner faced him directly), the patient looked at his own right hand and said "Well this is my right hand so this must be your right hand" and he pointed to the examiner's left hand, directly opposite his own right one. (He went through a similar performance when asked for the left hand of the examiner, only on his own left side.) The patient was an amiable man and he considered these examinations childish and laughable. He was prepared, however, to humour the examiner and did his best to co-operate. When shown the following figure and told that this was a person as seen from behind, and he must indicate the right and left sides, he consistently

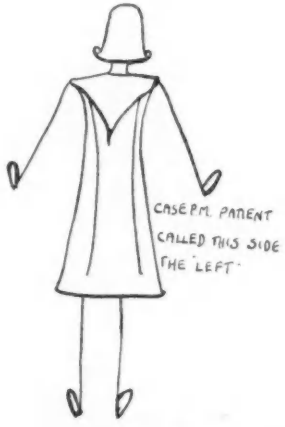

FIG. 19.

and with expressions of indulgent good will called the right hand the left and vice versa.

He was asked to write the numbers 1 to 10. He did this with a fine flourish, beginning at 1 on the right-hand side of the page and working rapidly across to 10 on the left-hand side. He was gently asked whether there was not something wrong with this and shown that the order was reversed. He thereupon dashed off the figures beginning with 10 on the right-hand side and working backwards to 1 on the left-hand side. He was asked to begin with number one. He then performed exactly as he had in the first instance, beginning with 1 on the right-hand side of the page and working across to 10 on the left-hand side. These figures are shown here:

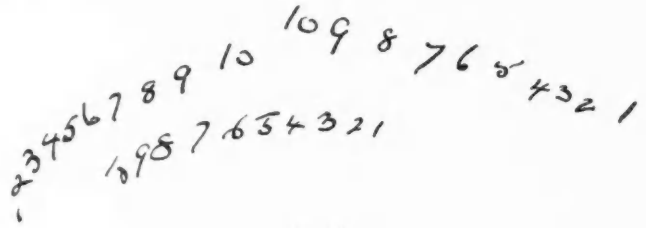

FIG. 20.

He was asked to draw a clock. Two attempts are shown, together with a picture of the patient's map of England and its relation to France. This patient spent most of his holidays abroad. It should be noted he spells France "Farnce." When asked to copy simple figures, however, he was able to do this correctly.

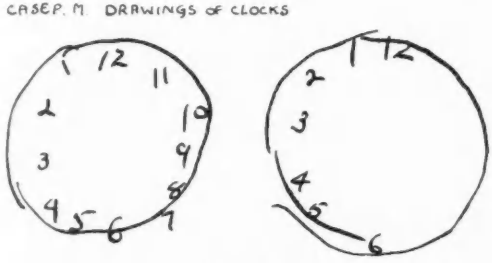

FIG. 21.

This patient was thought to have suffered a vascular lesion in the left parietal region. The Wassermann reaction and cerebrospinal fluid investigations revealed no abnormality. He was hypertensive, and on account of his age and the state of his arteries, it was thought unwise to carry out more intensive investigation. The patient's symptoms improved in a remarkable manner. He gradually lost the defects of disorientation. He was able to write and copy in a normal manner. He drew a clock-face perfectly correctly. He showed no confusion between right and left either in himself or others. His reading improved, although his right homonymous hemianopic field defect remained. He became aware of this particular impairment in his vision, complaining that he couldn't see as far to the right as previously—"as if a wall or a shadow blocked his sight." He no longer saw or acted "crossed."

This patient thus had a transient difficulty in projecting and rotating his mental

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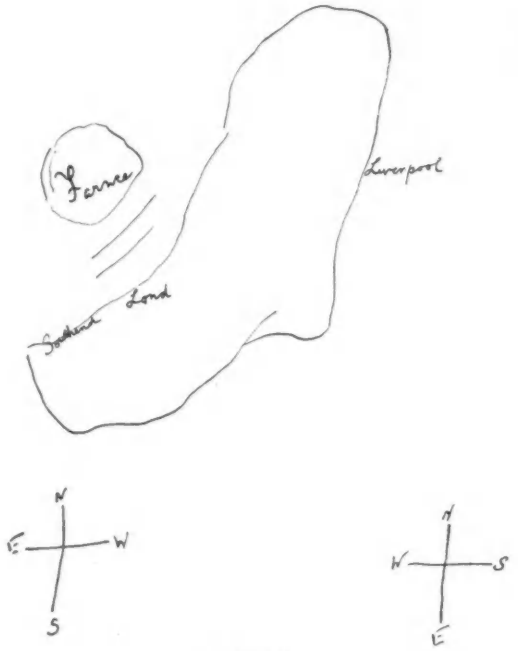

FIG. 22.

image of himself in space, together with confusion between the right and left sides of his body and objects in space. Head (1920) has mentioned that if "the examiner stands behind the patient and performs movements which the patient can see in a mirror, the patient is able to imitate movements which he is unable to imitate when the examiner performs them while standing directly opposite to him."

Case 4.—Mrs. M. Y. (N.H. No. 18025).

This patient, a right-handed woman of 39, was admitted to the National Hospital, Queen Square, under the care of Dr. J. St. C. Elkington. She had first been taken into another hospital "after having a fit in the street." The patient gave a history later of having had "blackouts" in one of which she was incontinent of urine in Ely Cathedral. She had been previously admitted to the National Hospital suffering from a profound disorientation which cleared up after a while. A diagnosis of hysteria had been made. On her present admission she was extremely dazed, apathetic, depressed and unco-operative. She complained of severe headaches and nausea. She suffered from a homonymous field defect on the left side. This was thought to be a complete hemianopia. She complained her left side felt queer and, while there were no changes in reflexes, she seemed to be suffering from a left-sided "sensory paralysis," with defect in recognition of postural change and position sense, and some impairment of appreciation of touch and pin-prick. She had difficulty in recognizing objects placed in her left hand. She walked with a curious gait, crossing the left leg before the right, so that she entangled her limbs, and frequently was in danger of falling. She complained of attacks of paræsthesiæ in the left arm and leg which lasted a few minutes at a time. The patient showed some interesting defects of orientation. She

was unable to recognize her bed in the ward, usually mistaking a bed on the opposite side of the room for her own. She eventually learned to know it by the dish of fruit and other objects she placed on the locker beside it.

Visual disorientation took the form of objects (and words when reading) moving towards one another and "going on top of one another." This movement made her feel sick. She also showed other forms of visual disorientation which are to be described in another paper. This patient also suffered from visual hallucinations of an ill-defined nature. She imagined she saw grey blurred objects, like animals, moving across her field of vision from left to right. These seemed to be approaching her "but never came closer." She also saw on one occasion grey waves moving across from left to right. The hallucinations were accompanied by a sense of great fear.

Writing and copying.—The patient on admission could write her name correctly, but upon being asked to write other words to dictation (with her right hand) she began to write from right to left across the page, with some of the words reversed as fig. 23.

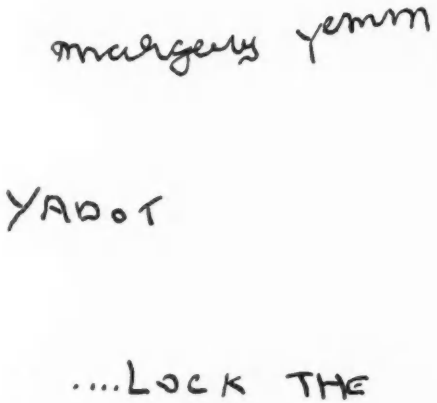

FIG. 23.

Writing was not always reversed and was at times normal. Other examples of disorientated writing are shown in fig. 24.

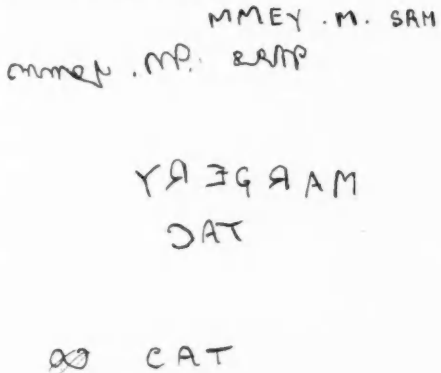

FIG. 24.

Here is an example of her copy of a given design:

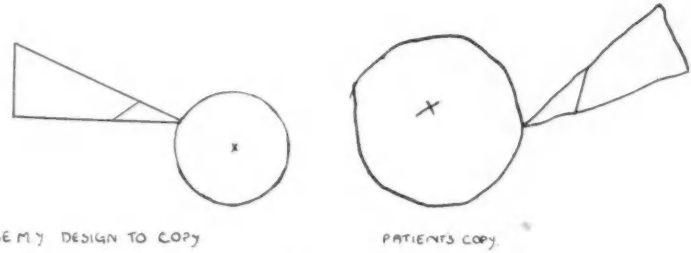

FIG. 25.

She was asked to draw a clock-face. On one occasion she began putting in the figures on the left-hand side of the clock with her right hand. At the mid-point of the periphery of the circle she changed hands and completed the right side of the figure with the left hand. On another occasion she drew this picture, the whole being performed with the right hand:

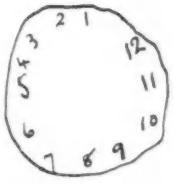

FIG. 26.

The stick test was performed as is shown in fig. 27.

Air studies and arteriography failed to reveal the site or nature of any cerebral lesion which might have been present. Lumbar puncture on two occasions showed 100 mg.% and 90 mg.% of protein but no other abnormalities in the C.S.F.

The patient's disorientation gradually improved but she suffered from an intense apathy and depression. The latter was so severe she was transferred to a mental hospital where she remained several weeks. During this time no treatment was given, but the patient's symptoms slowly improved and she was able to walk and find her way about.

After some months, during which the patient was able to earn her living as a children's nurse, her condition relapsed. She developed a severe headache, accompanied by pyrexia and vomiting. Repeated lumbar punctures again showed that her cerebrospinal fluid contained 90–100 mg. of protein. Her vision deteriorated. She complained of spontaneous tingling and burning sensations in the left arm and leg and an increasing "numbness" in these parts.

On examination there was a diminished appreciation of all modalities of sensation, but postural sensibility was the most markedly impaired. In addition, the patient had very great difficulty with the understanding of directions, particularly as regards the ability to make movements "to the right" or "to the left." She knew, however, which was her right hand and which her left.

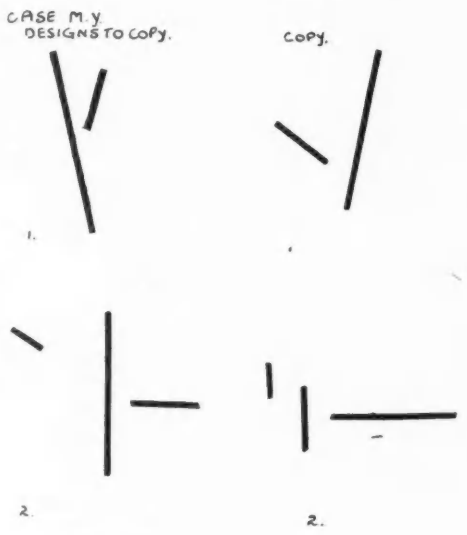

FIG. 27.

Her ability to appreciate sensation on the left side of her body became progressively impaired, and, as a result, the left limbs became increasingly "paralysed." Finally, the patient was unable to "feel" any form of sensation applied to, or arising from, that side. She was then unable to perform voluntary movements with the left arm or leg. She stated quite spontaneously, "This hand" (indicating the left) "doesn't mean anything to me. I look at it and I can see it, but it might just as well be somebody else's hand that's been chopped off and put here for me to look at."

The patient was asked to indicate her right and left hands. She raised the right and said: "This is my right." She then picked up her left hand with the right one and said, "If I was all right and could think properly, this would be my left, I suppose." The patient went on to say "When you talk about 'right' and 'left,' it sounds nonsense to me. All I know is I've got an arm and a leg" (indicating the right side), "it's called 'right,' but 'right' means everything to me that's going. This side does everything. It seems to do it automatically. All there is, is a right. 'Right' doesn't mean anything either—it's just this, just one. When I'm told to exercise, 'the other one,' I think what is there to exercise? It sounds so odd, I don't seem to be able to think it out. I'm living in one side. I'm trying to think where my other side has gone—if there *is* another side. I can't believe there is another side, and nobody could make me believe it."

On testing, the patient was unable to name the examiner's right and left hands, or to indicate objects to the right and left of herself. She stated that she could not think "what 'right' and 'left' meant."

At the time of writing, this patient's condition has not changed, and she is still in hospital.

Three other examples of disorientation may be briefly mentioned here. They occurred in patients in whom the pathology of the cerebral lesion is known.

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The first, *Case* 5 (N.H. No. 20303).

A right-handed woman of 37 years was admitted to the National Hospital, Queen Square, under the care of Dr. Denis Williams, complaining of "loss of driving force" and headaches from which she had suffered for about one year.

On examination she appeared to walk with a slow hemiplegic gait of which she was unaware. The disability was on the left side, and was in the nature of a sensory paralysis. Postural sense and awareness of position change were grossly impaired on the left, as were two-point discrimination, and judgment of solid form in the left hand. There was a slight impairment to all forms of cutaneous sensibility on the left side. Tendon reflexes were very slightly increased in the left leg. The plantar responses were flexor. This patient showed gross neglect of the left half of the body, and the left half of space with marked tactile inattention on the left, even for such a crude stimulus as a hand grasp. Drawings, both spontaneous and copied, were incomplete on the left side. An attention defect was present in the left visual field. The patient knew her right side from her left, but showed some hesitance and confusion when asked to touch her right and left ears and eyes. Testing was not very intensively carried out at that time but it was noticed that the patient performed the stick test as follows:

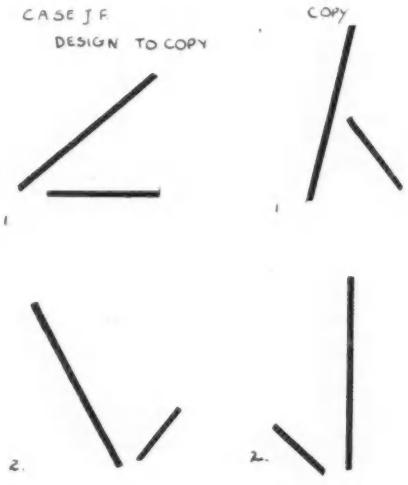

FIG. 28.

This patient was found to be suffering from a cerebral tumour and she subsequently died at the Royal Cancer Hospital. At post-mortem the tumour was found to be placed centrally in the cerebrum, overlying the third ventricle and extending into both hemispheres, more on the right side than the left. It replaced the right thalamus and caudate nucleus, and much of the right half of the corpus callosum reaching the internal capsule. On histological examination the tumour was said to have been a pinealoma but some controversy existed on this point.

The second, *Case* 6 (N.H. No. 35427).

A right-handed woman of 57 was admitted to the National Hospital, Queen Square, under the care of Dr. F. M. R. Walshe, suffering from headaches, confusion,

loss of memory, speech difficulties, a right homonymous hemianopia and a right-sided sensory paralysis. She also showed right-left disorientation to a marked degree. She was quite unable to distinguish between her right and left hands, and she had, in addition, a neglect of the right side. The speech disorder was not marked on admission, but increased as the patient's condition deteriorated.

When the patient was asked to raise her right hand, as often as not she raised her left, and vice versa. When asked to touch her right eye, she touched the left side of her forehead. On one occasion, when asked to raise her right hand, the patient looked around the bed and eventually raised the right hand saying "That would be my right hand before I lost it."

She was asked to imitate simple block patterns and failed hopelessly to produce anything resembling the original figure. She said "No—I can't do it, I always face the opposite ways . . . ." She suffered frequently from intense nausea and vomiting.

When she was asked to sit in a chair, the patient tried to climb into the chair forwards. She was quite unable to rotate her body so as to place her back against the chair seat before sitting, and had to be turned by the nurse forcibly and awkwardly.

Her confusion steadily increased so that it became impossible to examine her. She preserved a remarkable bright social manner in spite of a gross disorientation.

She was found to be suffering from carcinoma of the bronchus and at autopsy several cerebral secondary growths were found.

The third, *Case* 7.—H. W. (N.H. No. 23617). Dr. Critchley's case.

A man aged 63 years was admitted to the National Hospital, Queen Square, by one of us (W. G.), in a very drowsy state, complaining of headaches, giddiness, and loss of memory.

He was a small, thin, anxious man, who seemed to have some difficulty with understanding what was said to him. Concentration was poor, but once the patient was encouraged to concentrate upon the matter in hand, he was able to co-operate well. He made sensible replies to questions and relevant spontaneous conversation. He was able to respond promptly to such commands as "put out your tongue, give me your hand" (he proffered his right hand). He had some difficulty in closing his eyes to command, making fluttery movements of his eyelids "as if some apraxia were present." The patient knew his right and left sides and could name them correctly. He had a profound neglect of his left arm and made no spontaneous movements with it. He was asked to raise both hands, but he raised the right only. Asked to raise the other hand he looked puzzled and raised his right again. "Mr. W., you have two hands haven't you? This is one hand" (taking the patient's right hand). "Show me the other one." The patient seemed puzzled and looked around him for his other hand. Eventually he sighted the examiner's hand "There it is," he said. Question: "Is this *your* hand?" (moving the hand). Answer:"That's funny, the fingers are moving." Asked to put his handkerchief in his left-sided pyjama pocket, he searched in vain for this pocket on the right side. He said "Its gone—can't find it." The handkerchief was then placed in the pocket which was shown to the patient. A moment later he was asked to take the handkerchief from the pocket. Once again, he searched on the right-hand side and could not find the handkerchief. He made no attempt whatever to search on the left side. The patient stated he had noticed that when he has searched a long time for his box of matches he had eventually seen that he was holding them in his left hand.

Spontaneous weeping.—The patient at times burst into tears for no apparent reason and he would cry for a few minutes without seeming to be much distressed. He apologized for these outbursts saying he "could not help it—didn't know why he was crying, simply found himself in tears."

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On examination.—On confrontation the patient had a *left* homonymous hemianopia. On certain occasions during testing, he was asked to point to which hand was moving in his fields of vision and he consistently pointed to the hand in the *left* field of vision, when both hands were in fact moving. It was thought he had an attention defect in the *right field*. Later it was established the patient had a left homonymous hemianopia. He had therefore referred the stimuli from his right to his left field of vision in a manner similar to that in which he referred all sensory stimuli from the right to the left side of the body.

Sensory testing.—This was performed in the following manner: The stimulus was applied to the patient while he had his eyes *closed*. He was then asked to open his eyes and indicate the exact situation on his body where he had felt the stimulus. The patient co-operated well during this test. He complied with all instructions and did not allow his attention to wander. All stimuli (touch, pain and pressure) applied to the face, chest, arm and hand on the *right* side were repeatedly localized in an exactly similar position on the opposite (*left*) side of the body. The patient indicated the area where he believed the stimulus had been applied in a very prompt and accurate manner. The area always exactly corresponded to that on the *right* side where the stimulus had been applied.

Judgment of solid form.—When objects were placed in the patient's right hand while his eyes were closed, he was able to name them correctly. When an object was put in his right hand while his eyes were open he stated spontaneously "Funny—I thought I had that in *this* hand" (raising his left hand). Objects were then placed in his left hand and he was asked to name them (with closed eyes). He was quite unable to do so. On one occasion a long nail file was placed in the left hand and as the patient could not name it he was asked to open his eyes and look at it. He did so and while watching his hands he idly took the file in his right hand. An expression of alarm came over his face and he suddenly went through a curious pantomime, clutching the file first in one hand and then in another, muttering to himself: "Funny! Good Lord! That's got it!"—and it seemed that while he could *see* he was holding the file in his right hand, it felt to him as if it were in his *left* hand. He thus transferred it to the *left*. When in his *left* hand he could not feel it at all, so hastily put it back in the *right*, when once again he felt as if it were in the *left*.

This patient died shortly after admission. At autopsy, a large cystic glioma was found in the right parietal region. The tumour did not extend into the corpus callosum.

We were not able to confirm the site and nature of the pathological lesions in the brains of certain of the patients described above. In one or two of them, doubt has been raised that an organic lesion exists at all. The authors do not agree with the opinion that those patients without pathological confirmation are hysterical. Whether organic lesions were present or not, the disorders which we have described followed a well-defined pattern—as a comparison of the drawings alone will show, a pattern sufficiently constant for us to believe that it represents a disintegration of normal function.

Discussion

We have studied those aspects of orientation which are related to the ability of the individual to integrate all, and perceive certain, of the sensory inpulses arising from his entire body, and to compare one set

of information with another. We have suggested that man uses his knowledge of the position in space and the structure of his own body—that is, the sensory information which is derived from it—to measure the outside world. We have attempted to show that orientation in this sense is closely allied to movement. The individual is unable to make movements with any part of his body unless he is correctly orientated as regards the relation of the whole body to the parts and also to the outside world. This awareness need not occur at a conscious level. Movement greatly assists the individual's ability to orientate himself by increasing the flow of sensory impulses from the body and by extending the environment so that additional sensory material may be derived. We have suggested that complex skills such as writing, drawing, construction and so on, depend upon orientation as do the understanding and ability to use such language as connotes direction. In learning orientation, man, in ways directly related to his structure, also learns and accepts the three dimensional nature of his world.

We have stated that certain nervous integrations which assist a human individual to orientate himself in space never reach consciousness, but that others, which involve perception, depend upon previous and present individual experiences, which do at some time or other, occupy consciousness. After much repetition, the latter may become subconscious, and the orientative processes "automatic." Anyone who has watched a young child learning to stand upright and later to walk will know the earnest concentration which he devotes to the problem. Once learned, the faculty becomes subconscious and remains for life unless disordered by disease. Similarly, such complex functions as writing, spelling and drawing involve orientation at first at a highly conscious level, but later are "automatic," or nearly so. When a child first begins to write he must learn the conventions of his race and age. In the beginning, he does not know whether to write from right to left or vice versa, and his pencil strokes are incoherent. Letters and numbers are often reversed or upside down, and it is common experience to hear a child enquire which way a letter should go. Experience and teaching gradually bring order to the disorientation in a child's mind.

Finally there may be achieved the marvellous skills which can be seen, for example, in the works of da Vinci. In later life, disease may cause a patient to lose his carefully acquired ability to perform skilled movements, and also his understanding of the significance of direction, as described in our clinical cases. Lange, discussing Gerstmann's syndrome ("right-left disorientation, finger agnosia, acalculia, agraphia") put forward the theory that these difficulties were all related to "a general disturbance in the perception of direction." No doubt certain of the disorders which may occur in the performance of writing and also calculation may be attributed to this disturbance (illustrated by our patient Case 3), as may other disorders of voluntary movement. Even "astereognosis"

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may in some way be related to a disturbance in the perception of the direction of the planes on the surface of an object. "Dressing apraxia" probably involves the inability of the patient to relate his own shape and position to those of his clothes—he holds them and puts them on back to front or upside down. It may, of course, also be related to neglect or unawareness of one or other side of the body, and the patient may then try to put both shoes on one foot, or both sleeves of a garment on one arm. All these aspects of orientation, together with skilled movements, the special functions of writing, drawing, dressing, construction and so on, involve the ability of the individual to co-ordinate a mental with a motor performance and require learning.

Some processes which assist a human individual to orientate himself do not at any time reach consciousness. Liepmann (1920) said "Every voluntary action is based on an anticipatory plan. This plan has a specific structure. It contains not only the final aim, but includes also the ability to perform the single actions which are necessary for the realization of the plan. We are not consciously aware of all the single actions which comprise the plan." We have tried to show that these "single actions" depend upon processes intimately related to the organic structure of the body, and they may be called the substratum of orientation and movement in space. We have described them as being concerned with the central longitudinal axis and symmetrical lateral halves of the body, and have suggested that all movement takes place parallel to and in a rotatory manner around the axis. (While this pattern may have its conscious or subconscious psychological counterpart, we are not normally aware of the integrative processes of the nervous system which are necessary for the production of movement.) That this pattern of movement is perhaps a fundamental one is suggested by the movements which belong to the so-called "release phenomena," which occur as the result of disease of nervous tissue. These movements may take the form of tremors or athetotic writhings, in directions parallel to or rotating around the central axes of the body. Certain cerebral lesions are said to give rise to "turning movements" performed round and round the longitudinal axis of the body.

Finally, we wish to emphasize once again that the body as a whole and the entire nervous system are concerned with man's orientation and his movement in space. Movement is inseparable from orientation, orientation from movement, and both have their origin in sensation.

Summary

A study has been made of those aspects of human orientation in space which are related to the ability of the individual to integrate all and perceive certain of the sensory impulses arising from the entire body, and to compare one set of information with another. It is suggested that these aspects of orientation, which are entirely dependent upon sensation,

are allied to movement itself also dependent upon sensation. A hypothesis is put forward, stating that the body, limbs, and extremities possess central longitudinal axes on either side of each of which is placed a symmetrical but mirror-image half. The individual orientates himself according to this structure. Movement takes place in a rotatory manner about the central axes, and also parallel to them, and this pattern provides the basis for orientation. A series of patients suffering from various forms of disorientation is described. It is suggested that voluntary movement and certain functions such as writing, drawing, dressing, and construction, depend upon orientation and therefore upon the integrity of the entire nervous system.

Our thanks are due to the Physicians named in the text for permission to refer to case records of the patients under their care.

REFERENCES

AKELAITIS, A., RISTEEN, W., YORKE HERREN, R., and VAN WAGENEN, W. (1942) *Arch. Neurol. Psychiat.*, **47**, 971.

——, ——, ——, —— (1942) *Arch. Neurol. Psychiat.*, **48**, 914.

ALPERS, B., and GRANT, F. (1931) *Arch. Neurol. Psychiat.*, **25**, 67.

BERKELEY, G. (1709) A New Theory of Vision. Everyman Edition, No. 483. London: J. M. Dent & Sons Ltd.

BRAIN, W. R. (1951) Diseases of the Nervous System, London: Oxford University Press.

CRAMER, F. (1936) *Bull. Neurol. Instit. New York*, **5**, 37.

CRITCHLEY, M. (1928) Mirror Writing. Cambridge: Kegan Paul, Trench, Trubner & Co., Ltd.

GERSTMANN, J. (1940) *Arch. Neurol. Psychiat.*, **44**, 398.

GLEES, P., and COLE, J. (1951) *Experientia*, **7**, 224.

HAMMOND, W. A. (1881) A Treatise on Diseases of the Nervous System. 7th Ed. London: H. K. Lewis.

HEAD, H. (1920) *Brain*, **43**, 47.

HERRMANN, G. (1924) *Med. Klinik.*, **24**, 9.

HOLMES, G., and HORRAX, G. (1919) *Arch. Neurol. Psychiat.*, **1**, 385.

JACKSON, J. H. (1874) Selected Writings. Edited by James Taylor, 1932, Vol 2, 129. London, Hodder & Stoughton.

KRAMER, F. (1915) *Ztschr. f. d. ges. Neurol. Referate*, **11**, 379.

—— (1917) *Ztschr. f. d. ges. Neurol. Referate*, **14**, 58.

LANGE, J. (1930) *Monatsschr. f. Psychiat.*, **76**, 129.

LIEPMANN, H. (1920) *Ergeb. d. Med.*, **1**, 516.

PICK, A. (1922) *Psychol. Forsch.*, **1**, 303.

POTZL, O. (1918) *Wien. Klin. Wchschr.*, **31**, 745.

——, and HERRMANN, G. (1928) *Abhand. aus der Neurol.*, **46**.

RIESE, W. (1950) Principles of Neurology. Nervous and Mental Diseases Monographs, New York.

ROSENBERG, M. (1912) *Ztschr. f. Psychol.*, **61**, 25.

SCHILDER, P. (1935) The Image and Appearance of the Human Body. London: Kegan Paul, Trench, Trubner & Co., Ltd.

TRESCHER, J. H., and FORD, F. (1937) *Arch. Neurol. Psychiat.*, **37**, 959.

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THE CORTICAL REPRESENTATION OF MOTOR UNITS

BY

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LIDDELL and Phillips (1950, 1951), using single rectangular current pulses as stimuli, found that the most excitable area of the baboon's motor cortex was located in the middle third of the precentral gyrus. Stimulation of this region with weakest shocks (strength 1·0–1·6 ma., duration 5·0 msecs.) caused flick-movements confined to thumb, index and minimus fingers. Stronger shocks, even while still too weak to excite movements of other parts of the body, elicited flick-movements of the same digits from a larger area. Evidently the ventral horn cells governing these distal movements are, for some reason, more accessible to stimulation of the brain's surface than are those concerned with proximal limb segments. Such differential accessibility could depend on a richer anatomical representation, possibly by cells of individually lower threshold, in the cortex, and on denser synaptic connexions within the cervical spinal grey matter.

If it be supposed that some narrowly grouped colony of Betz cells forms the unique point of departure for the corticospinal pathway to the thumb-index-minimus motoneurones, the effectiveness of stimulation over a wider area is not easy to understand. Widely radiating dendrites could be invoked to explain it, were it not for experiments in which the foci of lowest threshold were excised without any weakening of response from the outlying regions (Liddell and Phillips, 1951). It is more likely that the cells of the colony are spread wide through the stimulable area, with a denser population of units in the area of lower threshold and a thinner population in the outlying zones of higher threshold. The existence of overlapping representation in the motor area is established by the anatomical work of Glees and Cole (1950).

Of what nature is the cortical representation of the spinal motoneurones, the ultimate units of motor function? Certain possibilities should be explored experimentally. An individual spinal motoneurone might be reached from Betz cells in an area of cortex more or less extensive. The synaptic pathways among spinal interneurones might then be numerous enough and close enough to one another to ensure that the motoneurones would discharge an impulse in response to each shock at the cortex, with small variation in latency. Or the synaptic connexions might be more diffuse, so that a motoneurone's response would be determined more by

physiological states than by anatomical connexions, and would be correspondingly labile.

At all times, consideration must be paid to complicating conditions due to horizontally spreading excitation of the types studied by Adrian (1937), Burns (1950, 1951) and Chang (1951). Collecting cells within the stimulable areas might feed excitation through synapses to the corticofugal cells, in which event, additional transmission delays should be detectable. Such delays would be further lengthened and varied by slow dendritic conduction over varying distances.

This paper describes myographic and electrical observations on some intrinsic muscles of the baboon's hand, made as a first approach to these questions. Myographic measurement of the magnitude of response was combined with electrical sampling of single motor units. The motor cortex was stimulated by single rectangular current pulses, as in our previous experiments, and the responses from different cortical points were compared.

Methods

Twelve West African baboons (*Papio papio, Papio strepitus*) weighing 4·0–12·3 kg. were the subjects of experiment. Hexobarbitone was the anæsthetic. The technique of preparation, of monopolar stimulation and of charting of the motor area has already been described (Liddell and Phillips, 1951). Single rectangular shocks of 5·0 msec. duration and strength 1·4–5·0 ma. were used.

In the first four experiments, latencies of action potentials in the thenar, hypothenar and first dorsal interosseous muscles were measured in simultaneous records. The leads were fine concentric electrodes (No. 20 hypodermic needles with stainless steel cores) connected to two differential condenser-coupled amplifiers and double-beam electron oscillograph. The shock artefacts were kept small by an earthed strip of silver foil which encircled the wrist subcutaneously. The moving photographic paper was time-marked by 100 c.p.s. flashes from a crater lamp, derived by dividing circuits from a 100 kc. crystal.

In the remaining eight experiments combined electrical and mechanical recording from one muscle was used. The first dorsal interosseous muscle was isolated except for its nerve and blood supply and its bony origins, and its tendon was attached by a steel hook to a frictionless isometric mirror myograph. The thumb and index metacarpals and the radius were fixed by screws to the heavy cast-iron myograph assembly. The limb was otherwise paralysed by section of the radial and median nerves in the arm, and section of the flexor carpi ulnaris tendon at the wrist. In some experiments the median nerve was spared and all the flexor tendons were cut at the wrist. The limb was enclosed in a thermostatically controlled moist chamber, maintained between 37·0 and 38·5° C. Action potentials of sample motor units were picked up by one or two silver-wire electrode-pairs (two 85μ diameter wires, about 0·1 mm. apart). With these, which were spring-mounted and moved by a rack-and-pinion arrangement, the muscle's bared surface was systematically explored until one or more clear-cut spikes were obtained when the muscle contracted. This technique permitted observation of the responses of the same motor units throughout a prolonged experiment, and without injury to the muscle.

The mirror myograph's movements were registered on moving photographic paper, time-marked by 100 c.p.s. flashes and with the instant and duration of stimulation signalled by a second crater-lamp. On to the same paper were also projected the oscillograph sweeps (repetition frequency 1·0 c.p.s.) to which the stimulating pulses

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were locked and on which the shock artefacts and action potentials appeared. The sweep velocity was frequently photographed with 1,000 c.p.s. pulses derived from the 100 kc. crystal, and in experiments in which only one channel of amplification was employed, was continuously monitored by 1,000 c.p.s. pulses on the second beam. Measurement of the records was facilitated by an instrument kindly constructed for us by Dr. E. H. J. Schuster. On the myographic time-scale measurement was accurate to $\pm$ 0·4 msec., and on the oscillographic time-scale it was accurate to $\pm$ 0·1 msec.

Results

(1) *Latency of electrical response of intrinsic hand muscles.*—The first four experiments were designed to test the possibility that movements resulting from stimulation of outlying cortical points might depend on the spread of deep cortical waves (Adrian, 1937) from fringes to centres of the areas. A preliminary survey showed no evidence of systematic lengthening of latency, a result already briefly reported (Liddell and Phillips, 1951).

In each experiment 57–215 trials were made from totals of 6–27 cortical points, some lying within the region of lowest threshold (1·4–1·8 ma.) and the remainder in the outlying higher-threshold zone (1·80-2·35 ma.). The points were stimulated and re-stimulated in random sequence, each receiving 3–12 shocks (duration 5·0 msec., frequency 1·0 c.p.s.) at each stimulation. Electrical records were taken from the thenar muscles in every case, and, in addition, from the first dorsal interosseous muscle in two experiments and from the hypothenar in one other.

The measured latencies varied from point to point, and from one and the same point, in an unpredictable fashion, ranging between 10·0 and 17·0 msec. There was no sign of systematic lengthening from points disposed *seriatim* along lines radiating from the lowest-threshold region of the cortex. Statistical examination of the latency measurements was kindly undertaken for us by Dr. D. J. Finney. In the first three experiments he found no significant difference between the means of measurements taken from points inside and outside the lowest-threshold zones. In the fourth, there was a significant difference: the mean of latencies got from the 19 outlying points exceeded the mean of the latencies from the 4 central points by 1·26 $\pm$ 0·35 msec.

But while experiments of this type would have demonstrated systematic latency lengthening if it had occurred, they did not allow us to follow the activity of single units for any length of time, because small movements displaced the electrode tips. The spikes first seen were soon lost in complex and variable action potentials. Further, cortical instability was such that the size of response, as gauged by watching and feeling the hand, varied from shock to shock, in spite of the "constant current" stimuli. Control of magnitude is important. In the spinal flexion reflex with its presumably simpler mechanism, Eccles and Sherrington (1931) found that the central latency shortened as the total excitation was made larger, and a similar relationship might be looked for with corticospinal excitations. Further experiments are needed for the elucidation of this problem.

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(2) *Combined myographic and electrical observations.*—In the remaining eight experiments the procedure was different, as already mentioned. An isometric myograph was used to measure the magnitude of the total response, and surface electrodes were applied to the exposed muscle, so that the spikes of one or more units could be recorded concurrently or consecutively for as long as two hours on end. The electrical responses could thus be compared at the same and at different sizes of total excitation.

The plan of the experiments developed with experience. At first, relatively small numbers of trials were made from large numbers of cortical points. When it was evident that there was no systematic variation of latency, but that the range of apparently random unitary latency varied considerably (fig. 1), a greater number of trials was made from fewer points. Nevertheless, the variability was still considerable, and there were no clear-cut differences between points. In the last four experiments, therefore, still larger numbers of trials were made and the performances of fewer points were compared.

(*a*) *Myographic features:* The first dorsal interosseous muscle was chosen because, unlike those of some of the thenar muscles, its origins are bony, so that adequate isolation and fixation can be achieved. It is not suggested that this muscle is "represented" in the cortex as such. But quantitative registration of its contractions provides an exact measure of the proportion of its motoneurone pool excited by each shock to the cortex, and this, in turn, is presumably some measure of the total spinal response, involving, in addition, at least thumb and minimus motoneurones. Myography of the thenar muscles would have been preferred, as the movements of the thumb have the lowest threshold in most experiments, while accompanying movements of the index and minimus fingers are more variable. Their threshold, in some of the present experiments, was higher than our previous experiments had accustomed us to expect for movements of thumb. It seemed possible, too, that the threshold was raised by continuous low-grade reflex inhibition resulting from the wounding of skin edges and deep tissues, and mechanical fixation of the limb, a drawback well recognized for this method.

The myographic records so obtained vary characteristically in size. Whether the stimulated cortical point lies inside or outside the lowest threshold region, the contractions elicited by a succession of identical single shocks vary greatly in height. Comparable responses for latency comparison have therefore to be selected from a large number of records. The initial tension was 8–12 grammes and the peak tensions of the contractions ranged up to 60 grammes.

In one experiment the contraction-times (Cooper and Eccles, 1930) of cortical twitches were compared with those of submaximal motor twitches of comparable size, set up by stimulation of the cut ulnar nerve

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at the end of the experiment, with the muscle temperature maintained as before. The motor twitch values lay between 26·0 and 29·0 msec. The 42·0–49·0 msec. contractions evoked by cortical stimulation in all experiments are the measure of an asynchronous motoneurone discharge. No systematic lengthening of myographic latency was found when points at a distance from the lowest threshold region were stimulated. The value was about 19·0 msec. in each experiment.

(*b*) *The responses of sample motor units:* 32 motor unit action potentials were studied in the course of the 8 experiments. Of these, 18 different spikes were recorded concurrently in pairs or larger groups (fig. 1), so that their independence of one another is established. A further 6 were also independent of one another, but may, in fact, have been derived from the fibres of one or more units recorded from alternative electrode positions on the same muscle. The remaining 8 were recorded individually from random electrode positions in four animals, so that their separate identity cannot be certain.

Examples are shown in fig. 2. It is difficult to be sure of their unitary nature when one of the most helpful criteria of "singleness"—that of even spacing of the spikes in repetitive responses to natural stimulation—is lacking. Granit and Ström (1951) point out that apparently single spikes recorded from ventral root filaments often turn out to be composite as an experiment proceeds. In the present experiments the spikes have sometimes varied slightly in configuration, probably because the base-line has been variably deformed by the activity of neighbouring units. But, on the other hand, in each of our records the spikes have "fired" or "missed" in all-or-nothing fashion (fig. 2). Records in which synchronous firing had occurred were accepted if algebraic summation of two spikes was undoubted: other records were discarded. A transparent positive print of the individual spikes, made on reversible film, facilitated the identification of the spikes in a long record. For the present purpose, it matters little whether a specific spike represents the response of a single motoneurone, or the responses of two or more which, under the particular conditions of experiment, are inseparably linked in function.

Some of the spikes were elicited at, or near, the threshold of contraction, and therefore represented the most accessible cells in the spinal pool: others began to appear in the larger twitches—cells on the fringe of the pool (Sherrington, 1931). The threshold tension-value for any unit was far from sharp, and could be described only in terms of the probability of that unit's response (number of responses/number of trials) between arbitrary limits of tension in a sufficient number of trials. Latency of response was apt to be longest and most variable near the threshold, and to be shorter, but still nevertheless variable, in the larger excitations. The shortening of latency in larger excitations is shown in the plots of

figs. 5, 6, and 7. Maximum and minimum latencies in all 8 experiments are shown diagrammatically in fig. 1.

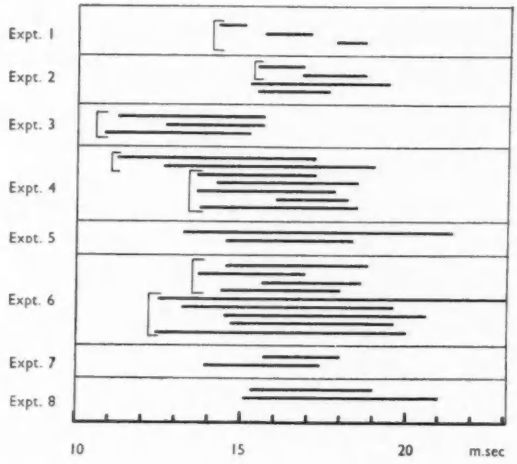

FIG. 1.—Diagram showing longest and shortest electrical latencies encountered in 32 motor units in the 8 experiments. Units recorded concurrently are marked by square brackets.

The responses of 24 of the units sampled were indistinguishable whether the cortex was stimulated in the lowest threshold area or outside it. Of these cells, 11 were low threshold and 13 higher threshold. There was no evidence that particular motoneurones might be "focus" cells for some cortical points and "fringe" cells for others. Evidence of differential corticospinal relationships is, however, afforded by analysis of the responses of the remaining 8 units. Illustrative examples follow.

The five motor units (*a*, *b*, *c*, *d*, *e*) shown in fig. 2 were recorded concurrently from the animal whose motor area is shown in fig. 3. 423 responses were collected from the 6 cortical points in the course of one hour. Twitches ranging between 25–50 grammes peak tension (initial tension 8·5 grammes) were obtained from all of the points: the current strengths are noted on fig. 3, from which it will be seen that points 1 and 2 had the lowest threshold. The stimulating pulses were of 5·7 msec. duration and were delivered in groups of 10–20 at one-second intervals. Points were stimulated and re-stimulated in the order 1, 2, 3, 6, 8, 7, with one-minute intervals between successive stimulations.

Fig. 2 (i) shows the configuration of the 5 spikes. Fig. 2 (ii–vi) illustrates their variable and mutually independent behaviour in five myographically indistinguishable responses (peak tension 35 grammes) evoked from point 1 of the cortex. Latencies and firing order are noted in the legend.

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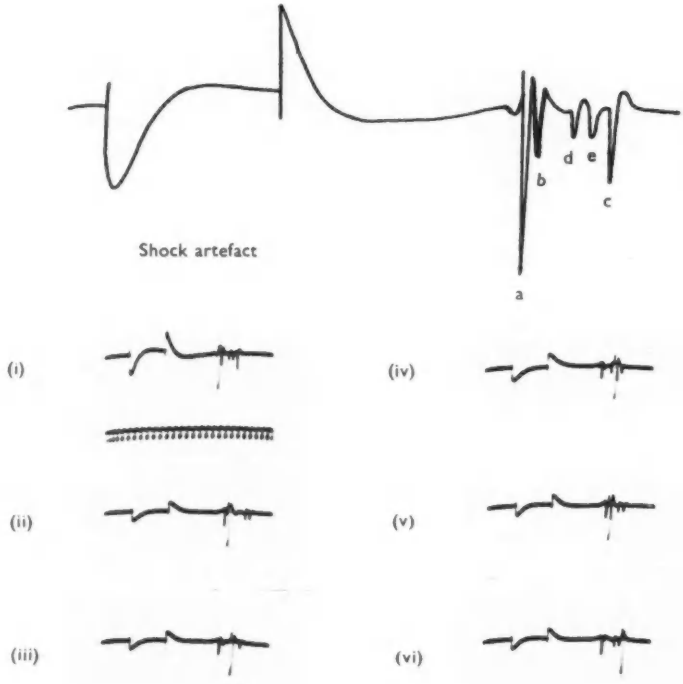

FIG. 2.—(1) Five motor units concurrently recorded in Experiment 6. Firing order *a*, *b*, *d*, *e*, *c* (*see* labelled diagram at top of figure). Time, 1,000 c.p.s. (ii–vi) Participation of same units in five responses of same total magnitude (isometric tension 35 grammes) elicited by stimulation of point 1 on the cortex (fig. 3). Firing order and latency (msec.) are noted for each record. (ii) *b*, 14·3; *a*, 15·0; *d*, 17·5; *e*, 18·2; *c* missed. (iii) *b*, 13·8; *a*, 15·8; *e*, 17·0; *c* and *d* missed. (iv) *b*, 13·8; *d*, 15·4; *a*, 16·0; *c*, 16·3; *e*, 16·9. (v) *b*, 13·9; *a*, 14·4; *c*, 14·8; *d*, 15·9; *e*, 16·7. (vi) *b*, 13·9; *d*, 15·9; *e*, 16·6; *a*, 17·2; *c* missed.

The fractions of fig. 3 (number of successes/number of trials) show the numbers of successful excitations of units *a* and *b* obtained from each point, and the numbers of sweeps in which the presence or absence of *a* and *b* spikes was certain. It is clear that unit *a* had its highest proportion of successes from point 1, and its lowest from point 2, 3·5 mm. away. Unit *b*, on the other hand, was equally accessible from both points. Both points were in the lowest-threshold area, and a similar range of twitch-tensions was obtained from each: in other words, similar-sized fractions of the total motoneurone pool could be excited from both cortical points, so that a generalized lack of response from point 2 is not in question.

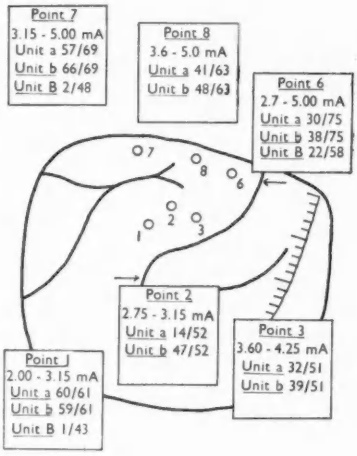

FIG. 3.—Tracing of photographic map of left motor cortex in Experiment 6. Lateral two-thirds of precentral gyrus exposed: central fissure marked by arrows: inferior precentral fissure to left of figure. Scale in mm. Current strengths employed, and number of responses/number of trials for certain sample units, are noted at each point.

The differential behaviour of units *a* and *b* is also demonstrated in the table, which shows that from point 2, *b* fired without *a* in 33/52 trials.

		Points					
		1	2	3	6	7	8
Total trials		61	52	51	75	69	63
Number of trials in which—							
Concordant response	*a* and *b* fired	58	14	26	23	57	35
	a and *b* missed	0	5	6	30	3	9
Discordant response	*a* fired, *b* missed	2	0	6	7	0	6
	a missed, *b* fired	1	33	13	15	9	13

and *a* never fired without *b*. From point 1, *a* and *b* both fired in 58/61 trials.

Such clear-cut differences do not exist in respect of the remaining points, as fig. 3 and the table show. Evidently unit *a* was less accessible from points 3, 6, 7 and 8 than it was from point 1, though not as inaccessible as it was from point 2. Unit *b* was most accessible from points 1, 2 and 7, and least accessible from point 6 (38/75 trials). Dr. D. J. Finney kindly examined these results statistically. He reports: "*a* and *b* are closely concordant in response, except from point 2. Of discordant responses point 2 seems to go in favour of *b* with very high frequency, points 3, 6

and 8 are about 2 : 1 on *b*, and others too few to discuss." Point 6 is noteworthy as showing the largest number of combined failures (30/75). Again, there is no question of a generalized lack of response from point 6, for the range of twitch-tensions was comparable with that from the other

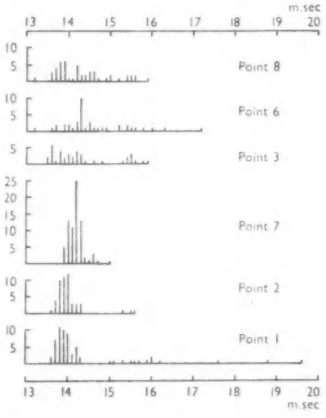

FIG. 4.—Unit *b*, Experiment 6. Number of responses at different latencies elicited from cortical points of fig. 3.

points. Fig. 4 shows the range of latencies for unit *b*. The values from the anteriorly placed points 1, 2 and 7, from which 59/61, 47/52 and 66/69 successes were obtained are obviously homogeneous, being grouped about peaks ; that for point 7 appears to be about 0·25 msec. later than those from points 1 and 2. From points 3, 6 and 8 (39/51, 38/75 and 48/63 successes) the values are scattered. For unit *a* the latencies were more widely scattered, and the values from the different cortical points showed no obvious differences.

Units *d* and *e* were low threshold "focus" units, with high probability of response, and showing no clear-cut differences between points. Unit *c* was a fringe unit, equally inaccessible from all points.

In the same preparation, 167 twitches were collected with the muscle electrodes in another position. Only points 6, 1 and 7 were stimulated. Four spikes (*A*, *B*, *C*, *D*) were concurrently followed. (They are not illustrated here, but *B* is referred to in fig. 3 and *A* in fig. 5). *A* was a "focus"spike, equally accessible from points 1 and 7: in the smaller responses (below 25·0 grammes) from point 6, however, the latency tended to be slightly longer, and the proportion of successes slightly less, than in comparable twitches from point 1 (30/37 against 28/29; fig. 5). Unit *B* (fig. 3) fired only 1/42 from point 1 and 2/48 from point 7 in responses exceeding 34·0 grammes tension, but from point 6 it fired 22/58 in responses above 24·0 grammes. *C* and *D* were "fringe" units, and gave no indication of differential accessibility or latency.

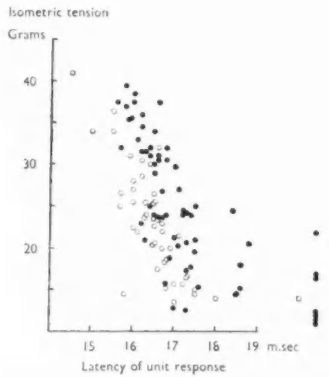

FIG. 5.—Unit *A*, Experiment 6. Latency/tension diagram. *Open circles:* responses elicited from point 1, fig. 3. *Filled circles:* responses from point 6, fig. 3. *Right of figure:* number and size of the responses from each point in which unit *A* failed to fire.

In this experiment, then, the performance of units *a* and *b* showed decisively that they were differentially accessible from points 1 and 2, which were 3·5 mm. apart on the cortical surface and both in a region of lower threshold. Unit *b* was a "focus" unit whether excited from either point: Unit *a* "focal" from point 1, "fringe" from point 2. Unit *b*, on latency as well as on probability of response, was more accessible from the anterior points 1, 2 and 7 than from the posterior points 3, 6 and 8. Unit *B*, a "fringe" unit, was most accessible from the higher-threshold point 6, while *A*, a "focus" unit concurrently recorded, was fired less often from point 6. The remaining 5 units (2 "focal," 3 "fringe") were not differentially accessible.

Fig. 6, taken from another experiment (Experiment 4, fig. 1), shows responses of a "focus" unit in which the latencies from the most laterally placed point (5) were longer and more variable than those from the most medial point (1). In responses below 20 grammes, 34/39 successes were obtained from point 5, against 28/29 from point 1. Both points lay outside the lowest threshold region (thresholds 2·7–3·7 ma.). Points 1 and 5 are decisively differentiated with respect to latency.

Units *A* and *B* of Experiment 8 were led from consecutive muscle electrode positions. Unit *A* was of "fringe" type, threshold-tension about 30 grammes. In responses exceeding this tension a higher proportion of successes was obtained from the higher-threshold points 1 and 3 (27/29 and 43/45) than from the lowest threshold region (26/46). Latencies were longest and most variable from the lateral point 3. Unit *B*, also a "fringe" unit, in responses below 35 grammes tension was fired less often from the lowest-threshold region (12/55) than from the higher-threshold point 3

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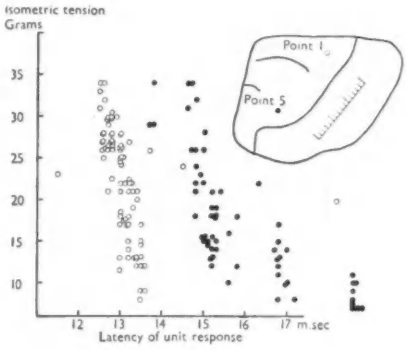

FIG. 6.—Experiment 4. *Above*, tracing of map of left motor area. Scale in mm. *Below*, latency/tension diagram for unit *A*. *Open circles:* responses from point 1. *Filled circles:* responses from point 5. *Right of figure:* number and size of responses from each point in which unit *A* failed to fire.

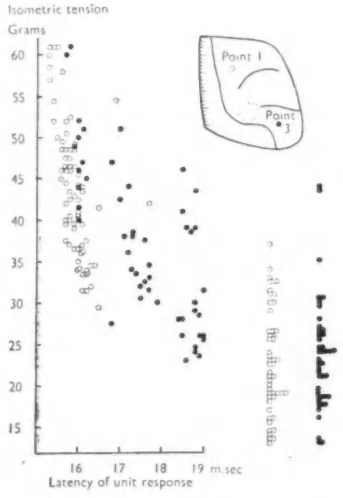

FIG. 7.—Experiment 8. *Above:* Tracing of map of right motor area. Lowest threshold region enclosed by dotted line. Scale in mm. *Below:* Unit *B*. Latency/tension diagram from points 1 (open circles) and 3 (filled circles). *Right of figure:* number and size of responses from each point in which unit *B* failed to fire.

(24, 66). Latencies were longest and most variable from point 3, with a suggestion of three peak values (fig. 7).

Unit *A* of Experiment 5 (not figured) was a "focus" unit, and at tensions below 30 grammes it fired in 41/53 trials from a point within the

lowest-threshold area, and in 27/31 trials from a higher-threshold point which lay 10·5 mm. medial to it, and separated from it by the superior precentral sulcus. Latencies were variable from these and from all other points tested, but were decisively longer from point 1 than from point 5.

	Point 1	*Point* 5
No. of observations	10	10
Peak tension	18–22 grammes	18–22 grammes
Shortest latency of unit *A*	17·0 msec.	15·9 msec.
Longest latency of unit *A*	19·1 msec.	17·9 msec.
Mean latency	18·26 ± 0·28 msec.	16·60 ± 0·28 msec.
Difference in means	1·66 ± 0·39	

Discussion

Theoretically, single-pulse stimulation offers the simplest conditions of artificial electrical excitation of the motor cortex, in that facilitation and "extinction" (Dusser de Barenne and McCulloch, 1937) should be minimal. Responses should not be complicated by slowly-cumulative "slow train" or "extrapyramidal" effects. Also the excitatory and inhibitory spinal reflexes generated by the brief muscular contraction would not yet have come into play, and would have subsided before the next serial stimulus. The strength and duration of the stimulating pulses were rigorously standardized. Nevertheless, it is hardly surprising that responses to successive shocks, even when applied to one and the same cortical point, should vary in total magnitude and in unitary characteristics (firing order, latency, presence or absence of response) to the extent seen in our experiments. For it is not as if quiescent corticofugal units were being stimulated, as peripheral axones are quiescent when they are stimulated in reflex experiments. Corticofugal units are excited by the spontaneous electrical oscillations of the cortex, and discharge brief trains of impulses in response to them, which, though they do not cause muscular contractions, must exert subliminal effects within the cord (Adrian and Moruzzi, 1939). An electrical shock may directly stimulate corticofugal units, whose apical dendrites are superficially disposed, but it may also act by the intervention of an active, surface-positive electrical reaction of the cortex, local and propagating (Adrian, 1937): the size, latency and temporal scatter of the resulting corticofugal discharge will thus depend on the state of activity of corticofugal and other cortical neurones at the moment of stimulation. Once they have left the cortex the impulses travel along axones which (in the cat) conduct at velocities ranging between 63·5 msec. and 18·0 msec. or less (Lloyd, 1941). In our animals the distance from cortex to last cervical segment was about 16·0 cm., so that if cat and baboon may be compared, a volley synchronously discharged would arrive in scattered order between 3·0 and 9·0 or more msec. later. In the spinal grey matter its effect would

Page 521, 5 lines from bottom:
For 63·5 msec. and 18·0 msec. *read* 63·5 m/sec. and 18·0 m/sec.

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be further variable: for asynchronous impulses would arrive at synapses distributed at levels at and upstream of the motoneurones, and in a lightly anæsthetized state the excitability of the post-synaptic cells would be subject to background fluctuations of unknown provenance. The size of the spinal motoneurone population excited by a single shock to the cortex, and the latency of firing of individual cells, must depend to an unknown degree on the operation of each of the foregoing factors.

Peripheral conduction time may be roughly estimated at 7·0 msec. Minimum total conduction time (7·0 msec. + 3·0 msec. corticospinal conduction time) would be of the order of 10·0 msec. Observed unitary latencies ranged between 10·8 msec. and 23·0 msec. in all experiments. 12·5–23·0 msec. represent the extremes of variation in a single experiment (fig. 1).

From the standpoint of myography, the variation in total response magnitude was apparently random, and there was remarkably little difference between the results from different cortical points. Similar-sized fractions of the motoneurone population can be called up by stimulation at any point in a large cortical area. But why are stronger shocks needed at outlying points? Stronger currents must, of course, diffuse more widely in the cortical tissue: we do not know how widely, or what density of penetrating current is needed to stimulate different cortical elements at different depths, variously orientated in relation to current flow. Against gross diffusion throughout cortex and white matter stands the absence of generalized motor reactions involving proximal limb joints in preparations in which the arm was not partially paralysed (Liddell and Phillips, 1951), and the noteworthy absence in the present experiments, even when 5·0 ma. currents were used, of the higher-threshold movements of proximal joints of leg and trunk.

It may be that the discharge of several corticofugal units is necessary for excitation of first dorsal interosseous motoneurones. An adequate number could be stimulated by a weaker shock to the lowest-threshold region if their distribution there were dense. If distribution in outlying-regions were sparser, a stronger shock would be needed to reach enough of them: in addition, those nearest the stigmatic electrode would be likely to respond with a high-frequency repetitive burst which would have a greater effect within the cord (Adrian and Moruzzi, 1939). In this way, access to similar-sized fractions of this motoneurone pool could be explained, but there would be no means of deciding whether the fractions are composed of the same, of overlapping, or of wholly different populations of spinal cells.

In 24 of the 32 units sampled, no difference was apparent between the responses from different cortical points. The motoneurone population in two such responses of given size could, therefore, have been one and the same. It might be that contractions elicited from a point 15 mm. away from the lowest-threshold region are due to excitation, by spread of

electric current, of the same corticofugal cells that respond to weaker shocks applied directly to that region.

But against this view is the evidence from the remaining 4 experiments when 8 units behaved differentially in responses of similar total magnitude called up from different cortical points. Such differential behaviour, persisting for two hours and more, must have a structural basis, and it is evidence of more or less selective stimulation in the neighbourhood of the stigmatic electrode.

For example, unit *b* (Expt. 6, fig. 3) fired in a larger proportion of trials from the three anteriorly placed points, 1, 2 and 7, than from the three posterior points 3, 6 and 8. This would imply denser synaptic connexions between this anterior field and the spinal motor nucleus. The same three points exhibit more homogeneous latencies than the posterior points 3, 6 and 8 (fig. 4). These also would be expected on the assumption of dense connexions: heterogeneous latencies would be probable if the spinal distribution of corticofugal axones were diffuse, at several interneurone levels. Whatever the explanation, the differences are specific for the particular points. Comment has already been offered on the differential behaviour of three other units, and on the undifferentiated accessibility of five others, in the same experiment. Evidence of differential response, specific for particular points, has also been provided for four further units in 3 experiments. Four units (Expt. 6, B; Expt. 8, A, B; Expt. 5, *A*) fired in a higher proportion of trials from higher threshold points than from the lowest threshold zone. These results are not explicable in terms of excitation of the lowest threshold zone by escaped electric current from outlying points.

Effects due to horizontally spreading intracortical excitation waves, travelling inwards from outlying stimulated points to the lowest-threshold regions, would have been readily detected in our experiments, particularly in the earlier ones in which, with this possibility in mind, larger numbers of cortical points were examined. In a typical experiment (Expt. 3—not figured) the distance along the cortical surface from the centre of the lowest-threshold region to an outlying point was 14·0 mm., but the superior precentral sulcus intervened to increase it. At 2·0 msec. conduction velocity (surface-negative wave: cat: Burns, 1950, 1951), the myographic and electrical latencies would have been lengthened by more than 7·0 msec. At 0·6–0·7 msec. (surface-positive: rabbit, cat and monkey: Adrian, 1937; surface-negative, monkey: Chang, 1951) lengthening by more than 23·0 msec. would have been observed. These responses have not been described to spread across larger distances than 10·5 mm. (Adrian, 1937), 10·0 mm. (Burns, 1950, 1951), and 5·0 mm. (Chang, 1951). Burns' (1950, 1951) surface-positive process appears to travel as far as 20·0 mm., but at only 0·1–0·2 msec.

No lengthening was detected myographically in the present experiments, and no systematic lengthening was seen in the responses of 26 of the 32

Page, 523, line 34:
For 2·0 msec. *read* 2·0 m/sec.
line 37:
For 0·6–0·7 msec. *read* 0·6–0·7 m/sec.
line 43:
For 0·1–0·2 msec. *read* 0·1–0·2 m/sec.

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units sampled. The remaining 6, however, showed characteristic latency differences as between certain points, ranging between 0·25 and 3·5 msec. (Expt. 6, *b* and *A*; Expt. 4, unit *A*; Expt. 8, units *A* and *B*; Expt. 5, unit *A*). Dendritic spread (Chang, 1951) or deep cortical spread (Adrian, 1937; Burns, 1950, 1951) over short distances could account for these differences. It is also possible that smaller corticofugal elements, with smaller axones, might be responding in the experiments in which the longer latencies came from laterally placed points, where the proportion of large pyramidal cells is known to be smaller (Economo and Koskinas, 1925).

Conclusion

We have explored (under hexobarbitone anæsthesia) the behaviour of individual spinal motor units in response to punctate electrical stimulation of the cortex cerebri of the baboon. Our immediate purpose was to test the degree of unvarying inevitability or of casual lability of transmission along this neural pathway, and through its synapses. Neither of these events is absolute, but both obtain partially. Sample motor units of M. 1st dorsal interosseous were activated by single pulse stimulation of different points of the motor cortex. Their responses were variable, fluctuating in latency and order of firing, or not firing at all. On the one hand, 24 motor units which we observed gave similarly varying responses although activated from different cortical points. On the other hand, 8 other motor units were activated optimally from particular cortical points. Thus we have not found more than a tendency to absolute or rigid relationship between any cortical point and a responding spinal motoneurone. There is, however, evidence that certain spinal motoneurones may be summoned into action with especial ease. But the order of their firing need not always be the same.

When the latency of motor-unit response is examined as the excitable cortical area is explored further from its middle (low threshold) and more towards its boundaries (high threshold) there does not seem to be any clear constant systematic lengthening of latency. This suggests that there need be, as a rule, no additional synapses on any horizontal path running to the middle (or low-threshold) part of the stimulable cortical area.

In brief, our experiments with anæsthetized monkeys are consistent with the view that the nerve pathway from the cortex to the ventral horn cells of the intrinsic hand muscles arises from all parts of the cortical area stimulated (e.g. fig. 7) and not only from its lowest-threshold part.

Acknowledgments

Mr. F. Elvidge assisted us with the experiments and Mr. A. Austin photographed the brains.

REFERENCES

ADRIAN, E.D. (1937) *J. Physiol.*, **88**, 127.
——, and MORUZZI, G. (1939) *J. Physiol.*, **97**, 153.
BURNS, B. D. (1950) *J. Physiol.*, **111**, 50.
—— (1951) *J. Physiol.*, **112**, 156.
CHANG, H-T. (1951) *J. Neurophysiol.*, **14**, 1.
COOPER, S., and ECCLES, J. C. (1930) *J. Physiol.*, **69**, 377.
DUSSER DE BARENNE, J. G., and MCCULLOCH, W. S. (1937) *Amer. J. Physiol.*, **118**, 510.
ECCLES, J. C., and SHERRINGTON, C. S. (1931) *Proc. Roy. Soc.*, B., **107**, 511.
ECONOMO, C. VON, and KOSKINAS, G. N. (1925) Die Cytoarchitektonic der Hirnrinde des erwachsenen Menschen. Vienna, J. Springer.
GLEES, P., and COLE, J. (1950) *J. Neurophysiol.*, **13**, 137.
GRANIT, R., and STRÖM, G. (1951) *J. Neurophysiol.*, **14**, 113.
LIDDELL, E. G. T., and PHILLIPS, C. G. (1950) *Brain*, **73**, 125.
——, —— (1951) *J. Physiol.*, **112**, 392.
LLOYD, D. P. C. (1941) *J. Neurophysiol.*, **4**, 525.
SHERRINGTON, C. S. (1931) *Brain*, **54**, 1.

XUM

KERNICTERUS

BY

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Part I.—The Natural History of Kernicterus

I have recently reviewed the cases of icterus gravis admitted to the Children's Hospital, Birmingham, between the years 1927 amd 1944 inclusive. The aim of the review was to find out the main sequelæ of hæmolytic disease of the newborn. Of the many families which I originally set out to trace only 10 were finally unaccounted for. I interviewed all children, if still alive, and their families. If the original diagnosis could not be confirmed serologically the case was discarded. Such confirmation was, however, obtained in 220 families. I soon realized that the only important sequel of hæmolytic disease of the newborn is kernicterus; many such cases were encountered, these were examined carefully and they, with 6 additional cases to which I was given access by colleagues, form the basis of this article.

(1) The Incidence of Kernicterus

The type of case of hæmolytic disease admitted to the Children's Hospital is highly selected, no case, for example, of hydrops fœtalis has come under our care because this hospital is not attached to a maternity hospital. To try to obtain a true indication of the incidence of kernicterus I have analysed, not the cases admitted to hospital, but the material provided by the families under review. The incidence of the various types of hæmolytic disease in these families is given in Table I.

Table I

Total number of families	220
Normal unaffected infants	433
Hæmolytic anæmia without clinical jaundice	19
Icterus gravis without kernicterus	242
Icterus gravis with kernicterus	72
Hydrops fœtalis and stillbirths	52
Miscarriages	58

The proportion of the various manifestations of hæmolytic disease in the 385 affected cases is given in Table II.

Table II

	Per cent
Hæmolytic anæmia without clinical jaundice	4·0
Icterus gravis without kernicterus	62·0
Icterus gravis with kernicterus	18·7
Hydrops fœtalis and stillbirths	13·5

None of these cases was given a replacement transfusion; simple transfusions of blood were given when the need arose. The incidence of kernicterus, 18·7 per cent, may err in two respects; it may be too low because cases of icterus gravis dying within the first week of life but not coming to autopsy may well have had kernicterus; it may be too high because some infants classified as normal may have been so mildly affected as to have escaped detection. The incidence is greater than that suggested by Diamond (1945), namely 16 per cent, but he gives no figures; it is lower than that given by Vaughan (1946) 27·7 per cent (20 cases of kernicterus out of 72 with hæmolytic disease) and by Claireaux (1950) 23·6 per cent (37 cases of kernicterus out of 157 with hæmolytic disease).

Once Rh iso-immunization has occurred the disease, it is generally considered, tends to be progressively more severe in successive Rh positive infants. If the first affected child has icterus gravis, the second may have kernicterus and the third be hydropic. This progressive increase in severity, however, is by no means constant. One mother, for example (in my material), whose first child was normal, gave birth to 6 successive children with icterus gravis; the first, second and fourth of these may have had kernicterus for each died on the third day of life, but the third, fifth and sixth all survived with no other treatment than the correction of anæmia by blood transfusion; another mother, whose first child was unaffected and whose second had icterus gravis, then had 4 successive stillbirths followed by a straightforward icterus gravis. Another mother had an uncomplicated icterus gravis treated by simple blood transfusions, after a case of hydrops fœtalis. In 7 of the families under review 8 perfectly normal and clinically unaffected but D-positive infants have been born after children with hæmolytic disease; in each instance the clinically unaffected child's erythrocytes, when suspended in bovine albumin, were agglutinated by the mother's serum; fortunately in no case was there any ABO incompatibility; one of these unaffected children was born after a child with kernicterus. Chown (1948) has also noted the delivery of a clinically unaffected Rh positive child after an affected child.

There is, however, a tendency for the disease to be more severe in successive Rh positive infants; e.g. of the first affected children with jaundice 43 out of 220 (19·5 per cent) had kernicterus; of the second affected with jaundice 17 out of 78 (21·8 per cent) had kernicterus; of the third affected with jaundice 10 out of 30 (33·3 per cent) had kernicterus. Cases of hydrops fœtalis and stillbirths are not included in these figures, hence the high proportion with kernicterus.

(2) The Onset of Kernicterus

Although yellow staining of the basal ganglia was first described by Orth (1875), and the term "kernicterus" was coined later by Schmorl (1903), to Esch (1908) goes the credit for first drawing attention to the

clinical features associated with the onset of kernicterus. In a typical case the baby, who has appeared to be clinically normal, apart from deepening jaundice associated with moderate enlargement of the liver and spleen, suddenly, between the second and fifth days of life, refuses feeds; he may at the same time become unnaturally quiet or he may, on the other hand, develop a high-pitched cerebral cry, the limbs may twitch and the head be thrown back; opisthotonus, rigidity of the limbs, more marked usually in the arms than in the legs, cyanosis, irregularities of respiration with periods of apnœa, the production of much frothy, often blood-stained mucus, and circulatory collapse usher in the end. Rigidity is not invariable and sometimes hypotonia may be the presenting feature; occasionally the former may be associated with a peculiar hardness of the muscles which simulates sclerema, and exceptionally the baby may become rigid as though carved in marble and it may even be possible to lift him up on the outstretched palm. There is usually a moderate elevation of the temperature and I have seen the temperature, pulse and respiration rates rise rapidly and in unison, as in the terminal phase of untreated tuberculous meningitis (Whytt, 1768). Generalized convulsions carry a grave prognosis.

The development of the above symptoms in a baby who, apart from deepening jaundice, had appeared to be lively and healthy, is very characteristic of kernicterus. The symptoms may develop with extraordinary abruptness and I have seen the transition from a neurologically normal to an obviously "cerebral" baby take place within as short a time as fifteen minutes. This baby, when lifted from his cot for a feed, was noticed to have some stiffness of the legs, but fifteen minutes earlier a careful clinical examination had revealed no neurological abnormality. He died thirty-six hours later and kernicterus was revealed at autopsy. This sudden alteration in the baby's behaviour occurs characteristically between the second and the fifth days of life; the more dramatic the change the more severely affected the infant. In my material this transition was noted in 52 instances; I have observed a similar transition in a further 8 instances; it occurred as follows:

On the 2nd day of life in 7 instances.
On the 3rd day of life in 24 instances.
On the 4th day of life in 17 instances.
On the 5th day of life in 10 instances.
On the 7th day of life in 1 instance.
On the 8th day of life in 1 instance.

The correlation between the day on which kernicterus makes its clinical onset and the immediate prognosis is illustrated in fig. 1; the earlier the onset of kernicterus the more certain is the child to die, the later the onset the more probable that the child will live.

37 of the 78 cases of kernicterus died within the first month of life, a further 10 were severely affected and died before reaching the age of

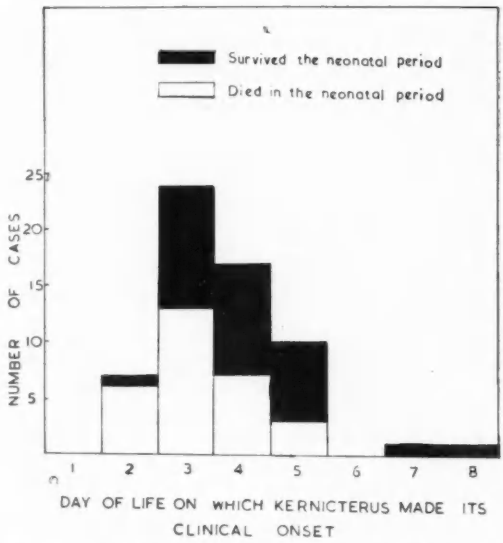

FIG. 1.—Kernicterus associated with Rh iso-immunization. The above figure gives details of the day of life on which kernicterus made its clinical appearance and the subsequent fate of the child.

3 years, 1 has died at the age of 20 years of pneumonia, but 30 are still alive and all are more than a year old. This is a higher survival rate than that given by either Vaughan (1946) or Claireaux (1950). 14 of Vaughan's 20 cases died in the neonatal period and a further 2 in infancy, only 4 survived. 33 of Claireaux's (1950) 37 cases died in the neonatal period and a further 2 in infancy, only 2 survived. The higher survival rate in my series may be due to the care with which cases have been followed up, but the proportion surviving may be rather less than the figures suggest, for only verified cases of kernicterus are included among those who died.

The distribution of deaths during the first ten days of life is given in fig. 2; 3 additional deaths occurred during the next two weeks.

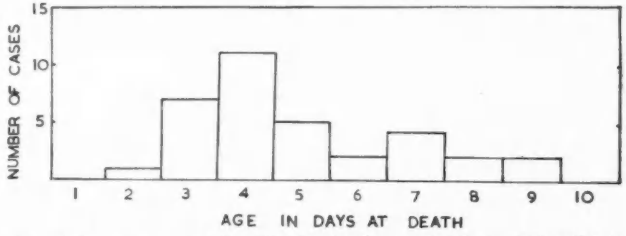

FIG. 2.—Kernicterus associated with Rh iso-immunization. The distribution of deaths in those dying during the first ten days of life.

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Death is seen to occur most commonly on the fourth day of life, as Claireaux (1950) also found.

I have emphasized the findings associated with the onset of kernicterus but, it may be asked, can a baby exhibit these and then develop normally; can an infant during the first week of life be clinically a case of kernicterus and then later, when two or more years old, be neurologically normal? I have never seen this occur nor, Crosse (1950) tells me, has she. The reverse, however, is occasionally true, a baby may appear to be normal during the neonatal period and yet later prove to be a case of kernicterus; such cases are not usually severely affected. More frequently kernicterus is suspected during the first week of life but the infant's condition thereafter improves so much that, at the age of 3 or 4 weeks, it is thought that he is not a case of kernicterus after all. The first case cited by FitzGerald, Greenfield and Kounine (1939) illustrates this well, and one of my cases, although she had been reluctant to take her feeds on the fifth day of life, was thought, when she was a month old, to be a normal infant; seven months later she presented with marked head retraction and opisthotonus and her limbs were rigid. Sometimes attention is focused so exclusively on the associated hæmatological and biochemical changes that no neurological abnormality is either looked for or suspected, but when the mother is allowed to handle her own child she notices that his behaviour is abnormal, and that, for example, he arches his spine or jerks his head back.

It is important to watch the infant carefully during the first 10 days of life; if any abnormality is noticed the child should be seen every now and then until he is at least 1 year old, so that, should he have any neurological sequelæ, especially deafness, this may be noted early and the parents given the necessary advice and help in bringing up their child.

One infant, for example, was not thought to be a case of kernicterus in the neonatal period; he had been drowsy on the fourth day of life but in all other respects had appeared to be a case of uncomplicated icterus gravis. He was seen again six years later; at this time his parents were quite sure that he was a normal, albeit highly strung child who was backward only in talking, for his vocabulary was still limited to a few words; he first sat up when he was 8 months old and he first walked when he was 2 years old; he walked very unsteadily at first and his legs were, on this account, put in irons. At the age of 6 years his movements were choreic and he had an appreciable perceptive deafness in addition to his obvious emotional instability. This deafness was not suspected by the parents.

5 other children with kernicterus were thought to be normal when they were discharged from hospital at the ages of 2 to 3 weeks; the suggestive signs in these were an inability to suck vigorously on the fourth day of life in one instance, a cyanotic attack on the fourth day of life in a second, and rolling movements of the eyes on the fourteenth day of life in a third; 2 seem to have shown no neurological abnormality in the neonatal period; both these are minimally affected; 1 is, however, quite deaf, and the

other has a high frequency perceptive deafness associated with involuntary movements of the choreic type.

Involuntary movements and abnormalities of muscular tone, if and when they occur, are soon noticed and quickly bring the patient to the doctor, but deafness, especially when it is partial, is frequently missed. As one mother naïvely expressed herself: "The deafness is so perceptive you cannot perceive it."

One child, not included in the writer's series of cases of kernicterus because he has perfect control over all his movements, was originally thought to be a case of uncomplicated icterus gravis; jaundice appeared when he was 12 hours old and persisted for three weeks, he became anæmic and was given a blood transfusion. He did not take feeds eagerly in the neonatal period and he cried repeatedly until he was a year old; he first sat up when he was 9 months old and walked nine months later. His parents had such difficulty in training him that they concluded he was mentally retarded, until one day, when he was 4½ years old, he played with an alarum clock which suddenly rang. The sudden clatter made everyone in the room jump, everyone, that is, except the "mental" child, who continued to play with the clock as though nothing had happened. His parents instantly realized, and for the first time, that he was deaf.

If the infant who develops kernicterus is watched with sufficient care during the first ten days of life there is almost always some indication of the presence of kernicterus. Gross signs of kernicterus cannot be overlooked, but in the less affected cases there may only be a transient reluctance to feed, a transient drowsiness or occasional rolling movements of the eyeballs. It is to those who feed, handle and hold these infants during the first ten days of life, rather than to those who subject them to a full neurological examination that, in the mild cases, the presence of kernicterus is revealed.

(3) Kernicterus in Those Surviving the Neonatal Period

The first case of kernicterus surviving the neonatal period was recorded by Arkwright (1902), in the year preceding Schmorl's (1903) publication. The first child in the family described by Arkwright developed neither jaundice nor anæmia but died at 7 months of age. The 14 children born subsequently all had a severe neonatal jaundice; the second and fourth survived, the third died in infancy still jaundiced, the fifth, sixth, seventh, eighth, ninth, tenth and eleventh all, except one who bled from the navel, died with convulsions in infancy. The twelfth and thirteenth died at 16 and 7 months respectively. The fourteenth, a boy, developed jaundice on the second day of life which persisted for a fortnight; at the age of a year he had "no use in the legs," but at 2½ he could stand and walk round a table whilst holding on to it, but his knees were very weak and his knee-joints almost flail-like.

Guthrie (1913) was the next to record a child surviving with kernicterus. The subject was a girl, the eighth child in a family, the third, fourth, fifth, sixth and seventh all having had a severe neonatal jaundice. She

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herself was jaundiced at birth and remained so for the six subsequent weeks. She was shown, when 19 months old, at a meeting of the Royal Society of Medicine. She had never been able to sit up, stand or walk, she had a vacant expression and her speech was limited to "mum, mum"; the musculature was hypotonic; the body and limbs exhibited constant varying movements resembling those of chorea, but much slower, and best described by the term "choreo-athetosis." During the discussion which followed the demonstration Parkes Weber remarked that, if Dr. Guthrie's explanation of the choreiform movements in the child in question was correct, namely that they were the result of the same kind of lesion in the basal ganglia as had been found in fatal cases of kernicterus, the case would probably be the first one to show the late results after recovery from the initial symptoms.

Spiller (1915) recorded 4 more cases. Hart (1925), when describing the family history of an infant on whom he had performed, very successfully, an exsanguination transfusion, mentioned that the second child in the family, a girl, who had been deeply jaundiced until 12 months of age, was at the time of writing, twelve years later, suffering from chorea. Many cases have since been reported, the two largest series being those of Evans and Polani (1950) who collected 16 cases of kernicterus surviving the neonatal period, and of Pentschew (1948) who collected 18 cases, many of the latter were not associated with Rh iso-immunization. The largest series previously reported was that of Lande (1948), who gives details of 8 cases. She suggests that cases of kernicterus fall into one of four main groups:

(1) Those with generalized athetosis.
(2) Those with persistent spasticity.
(3) Those with ataxia and disturbance of balance.
(4) Those with an atonic diplegia.

But Evans and Polani (1950) and Pentschew (1948) rightly draw attention to the changing picture exhibited by cases of kernicterus; the former state, for example, that opisthotonus is often present during the first months of life but is uncommon after the age of 1 year while irregular movements are uncommon in the first two months of life but are present in most cases over the age of 3 years, and that 80 per cent of the older patients exhibit chorea, choreo-athetosis or athetosis; hypotonia, which is not in evidence during the neonatal period, is a striking feature of the condition between 6 and 18 months of age and unusual later. Lande, and Pentschew, and Evans and Polani have drawn attention to the two main aspects of this disorder for, as Lande suggests, there are certain characteristic types, and yet each type has its own characteristic development.

For descriptive purposes I have subdivided my cases into three groups.

Group 1 are those who are most severely affected; they develop a

generalized and remarkable rigidity at an early age and die in infancy. 10 of my 41 cases fall into this category.

Group 2 also develop a generalized rigidity, but on to this are grafted involuntary movements, giving the clinical picture of dystonia, the condition does not appear to be sufficiently severe to jeopardize life. 3 of my cases fall into this category.

Into Group 3 fall the majority of the cases of kernicterus, 28 of my 41 cases; rigidity is usually absent and if present is not disabling, the involuntary movements are choreic, choreo-athetoid or athetoid in nature. The features of these groups, in greater detail, are as follows:

Group 1.—Into this group fall all the most severely affected cases. 10 examples were encountered in my survey, 3 only were examined personally, for the remainder had died. All developed a generalized and remarkable rigidity at an early age and all died in infancy. The clinical onset of kernicterus, between the second and fifth days of life, was always dramatic, gave rise to considerable anxiety, and was associated with the sudden refusal of feeds. Head retraction and opisthotonus, though usually not noted at the onset, developed in each case from infancy and were associated with the development of a generalized and extreme rigidity of the limbs and trunk. This rigidity was first noted as early as 4 weeks and as late as 8 months; in 3 instances it was fully developed at 6 weeks, in 1 at 4 months, in another at 5 months, in 2 instances at 6 months and in 1 at 7 months. With the advent of the rigidity the infant usually lies in his cot in a position of opisthotonus with the head thrown back, the legs fully extended, the arms adducted at the shoulders and flexed at the elbows and the fists clenched, a position analogous to that of the decorticate primate (Magnus, 1926). The rigidity and opisthotonus are most in evidence when the infant is handled, and mothers find the dressing and undressing of such infants difficult. In 2 instances only was there a transient hypotonia before the development of the rigidity. In a further instance hypotonic interludes punctuated the more persistent rigidity and opisthotonus.

Twitching, jerky movements developed in all cases, in 2 as early as the third day; in the 2 infants who lived to be over a year old the movements were described before death as being jerky and athetoid. Rolling movements of the eyeballs occurred in 6 cases. Convulsions also occurred in 6; in 2, both of which had further convulsions, at the clinical onset of kernicterus; in 4 they were terminal. Irregular breathing was noted in 2 cases and was associated in 1 with periods of cyanosis. Profuse perspiration, in the absence of any fever, was noted in 3 infants and in 1 of these the perspiration was so persistent and excessive that the cot blankets had to be changed several times a day. An irregular fever (rising to 106° F. in one instance) in response to minimal infection, and even in its absence, occurred in 4.

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The main characteristics of this group are a severe onset followed by the development of generalized and extreme rigidity with head retraction and opisthotonus, twitching movements of the limbs and evidence of an associated autonomic imbalance in the form of irregular fever, and bouts of excessive sweating.

Cases which seem to fall into this group have been recorded by the following:

(1) De Lange (1924): an infant who developed generalized rigidity prior to death when 6 weeks old; the jaundice in this instance was associated with an umbilical infection.

(2) Zimmerman and Yannet (1933 and 1935): a child, dying at the age of 3 years, who developed a generalized rigidity with athetosis and who, for the last four months of her life, ran a persistent fever, rising on occasion to 106° F., in the absence of any manifest infection.

(3) van Westrienen (1935 and 1936): this infant became extremely rigid and at the same time restless, perspired frequently and, for three months, ran a high remittent fever which subsided gradually with the exhibition of atropine. Death occurred at the age of 1 year.

(4) Giuntini (1942), Case 1: generalized rigidity made its first appearance at the age of 3 months and was associated with opisthotonus and jerky athetoid movements. Death occurred at 10 months as the result of an acute infection.

(5) Lande (1948), Case 7: this infant developed head retraction and generalized rigidity, which persisted, on the fifth day of life. Frequent jerking movements of the limbs and periods of relaxation were present at the age of 10 months, at which time she ran a high remittent fever, often up to 104° F. or 105° F., which did not subside with penicillin medication; terminally the temperature rose to 108·5° F. She died of bronchopneumonia at the age of 1 year.

(6) Yannet and Lieberman (1946), Case 2: this infant developed head retraction on the third day of life and, in infancy, was frequently seen by physicians because his temperature was so high; sometimes there was an associated respiratory infection, sometimes there was not; frequent blood cultures were sterile. At the age of 3 years the muscle tone was, for the most part, hypertonic, but sometimes it was hypotonic. The child died at the age of 3; a small quantity of thick pus was found in the right mastoid air cells post mortem.

The following cases may also, though less definitely, be included in my group 1.

FitzGerald, Greenfield and Kounine's (1939), Case 1: this child refused feeds on the third day of life and on the fifth day developed a temperature of 105° F., head retraction and convulsions, in which she assumed a position of opisthotonus; peculiar movements of the eyes in which the eyeballs rolled up and down developed when she was 8 weeks old; at this time the upper limbs were rigid. She died of an intercurrent infection at the age of 4½ months.

Sobel and Zucker's (1940) case: she died at the age of 3 years of pneumonia. She first exhibited opisthotonus, then a generalized and marked rigidity and later purposeless writhing movements of all four limbs, choreo-athetoid in character.

Claireaux's (1950) case which developed opisthotonus and early rigidity and died at the age of 4 months.

I think this group is a real one: all cases are strikingly similar and death, sooner or later, terminates the distressing syndrome. The rigidity is described by van Westrienen (1935) as lead pipe in character and by Giuntini (1942) as extrapyramidal or parkinsonian; in my experience

van Westrienen's description is the more typical: the limbs are extremely rigid, the muscles, when stretched, yield as it were reluctantly, the rigidity is persistent and plastic and is neither clasp-knife nor cogwheel in character. Thermal instability is also a prominent feature of many cases and was present in 4 of my 10 cases as well as in 4 of the 9 cases cited above; the temperature often rises in the absence of any obvious infection, and in the presence of an infection tends to rise to greater heights than would be anticipated. The temperature was not influenced by penicillin in Lande's (1948) case and in one of mine yielded only slowly to both penicillin and sulphonamides.

Group 2.—3 of my cases,[1] are included in this group. These 3 are severely handicapped physically and cannot sit up, stand or walk by themselves. Their symptomatology has much in common with the cases in group 1, except that none show any thermal instability, nor does the condition appear to be sufficiently severe to jeopardize life. Opisthotonus and head retraction developed, in each case, in infancy, and rigidity had fully developed by the age of 4 months. Before the development of the spasticity one child was hypotonic; her neck muscles are still, at the age of 6 years, lacking in tone and she still cannot hold her head up for more than a few seconds at a time. These 3 cases are excitable and they exhibit continuous twisting and writhing movements of the trunk and limbs, more akin to dystonia than to athetosis: they have little if any real control over their limbs. The involuntary movements and the spasticity are increased if the children are under any emotional strain; they subside completely during sleep. I have not been able to demonstrate the neck-righting reflexes in these cases but in 2 the "magnet" reaction can be easily elicited.

Similar cases have been reported by Spiller (1915), Case 4, and by Ford (1945). Yannet and Lieberman (1946) record a case (Case 6) which resembles these cases in some respects but not in others.

Spiller's case was nearly 4 years old. She could not hold her head up, nor could she sit up without support; all her limbs were extremely rigid and this rigidity was such that none of the tendon reflexes could be obtained.

Ford's case was 6 years old. He had never been able to walk, to stand or even to sit up, without support; involuntary athetoid movements of the face, arms and legs were present and these were associated with an intense muscular rigidity; when the patient relaxed the rigidity would sometimes disappear and the movements subside.

Yannet and Lieberman's case (probably, they assert, a case of kernicterus) was a girl 7 years old; she developed head retraction on the third day of life and increased muscle tone four months later; this rigidity persisted, became more widespread and could only be overcome with difficulty; in this respect she resembles my 3 cases. The tendon reflexes, however, were exaggerated, there was bilateral ankle clonus, extensor plantar responses and an absence of involuntary movements; in this respect she is far from typical.

Group 3.—Most cases of kernicterus surviving the neonatal period are

[1] 1 has recently died at the age of 20 of pneumonia.

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not so severely handicapped as the three instances given above and included in group 2. Rigidity is usually absent and if present is not disabling; the child learns in due course to sit up, to stand, to walk and even to run; the involuntary movements, which are always present to a greater or less extent, vary from the choreic through the choreo-athetoid to the athetoid. Evans and Polani (1950) state that, of the older patients, 80 per cent show athetosis, choreo-athetosis or chorea and in my material 28 of 31 cases (approximately 90 per cent) do so.

In a typical case the child's development is as follows: after the onset of clinical kernicterus, between the third and eighth days of life, the infant's condition improves and, apart from intermittent head retraction and rolling movements of the eyeballs, he may appear to be normal, or almost so, at the age of 4 to 8 weeks. Soon, however, it becomes apparent that the musculature of the limbs, neck and trunk is hypotonic; when the infant is lifted up, the head, unless supported, drops heavily back, the trunk muscles are toneless and the mother complains that her baby is "floppy"; if she tries to sit him up his body sags, like a doll from which the stuffing has been removed. With the advent of the hypotonia, or sometimes a little later, but usually between the second and the ninth months, involuntary movements make their first appearance; the infant becomes restless, he is never still, except when he is asleep, and his movements become jerky; he behaves, as one mother described it, as though subjected to a series of electric shocks. When the child reaches the age of a year the movements begin to take on a choreic or athetoid texture which is often not fully developed until he is 3 or even 5 years old.

The child usually learns to hold his head up between the sixth and twenty-fourth months, and learns to sit up between the eleventh and twenty-fourth months; when he first sits up he wobbles, like a ship on a stormy sea, but as the tone of the muscles improves he becomes steadier, learns to stand and then, between the ages of 2 and 3 years, begins to walk. Learning to walk for the child with kernicterus is a more painful and protracted procedure than for the normal toddler. The child with kernicterus is usually ataxic and for several months, before he dares to stagger unsupported across the room, he clings to the furniture for support. When he finally ventures forth by himself he falls repeatedly and much more frequently than his normal counterpart; but, usually within six months of first trying to walk, his gait becomes steadier, the ataxia subsides and the chorea, choreo-athetosis or athetosis become fully developed. Thereafter there is a tendency for the involuntary movements to subside; this improvement occurs *pari passu* with the development of emotional control. The involuntary movements, however, may increase in severity if the child is subjected to any emotional strain, and illness also would seem to cause an exacerbation of the symptoms, for in one child, after a burn, the involuntary movements became for a while more disabling than they had ever been. The aggravation of the

involuntary movements by emotional strain makes the acquisition of emotional control doubly desirable in cases of kernicterus, not only for its own sake but also for the diminution in the involuntary movements which follows, but the acquisition of emotional control is no easy task, for virtually all cases are unusually unstable emotionally; only one child in my series has a phlegmatic disposition, and his physical handicap is minimal. The gradual suppression of the involuntary movements is only seen in the older children; one child, for example, at the age of 8 years was choreic, her movements were jerky and her writing was slow and uncontrolled; now, at the age of 21, she exhibits little if any evidence of chorea, she can write clearly and she can even embroider. Another who was athetoid at the age of 5, is now, five years later, choreic. I was surprised when I began to review the older cases of kernicterus to find them less handicapped physically than I had expected; the parents themselves commented on the great improvement in co-ordinate movement which their children had experienced. Allan (1950), who has had the orthopædic treatment of many athetoids under his care, states categorically that they tend to improve. Evans and Polani (1950) record one instance (Case 11) which seems to have deteriorated; this child was choreic at the age of 5 and a mild athetoid at the age of 8. Apart from the remissions associated with emotional upsets and illness the cases in this group tend, in my experience, to improve. By contrast the severe cases with marked spasticity in group 2 have shown virtually no improvement in their physical control.

The above gives a composite picture of the phases through which most children with kernicterus pass; there is considerable variation in the individual case and in what follows I have analysed the cases in greater detail.

Rigidity.—A variable degree of rigidity was noted in 5 children; it was first observed between the second and eighth months, before the infant could be expected to exert any voluntary tension. 4 other children were occasionally stiff in infancy but the only one who is now fully grown has no residual tension. Evans and Polani (1950) have also noted that the muscular spasm which may be associated with athetosis usually appears before or with the athetosis and not as a later addition. The intermittent rigidity associated with opisthotonus seen in infancy does not persist once the child has learnt to stand, and it often subsides earlier. The generalized rigidity seen in the 3 cases in group 2 has persisted and shown no signs of subsiding, except during sleep, whereas the rigidity which 2 of the older athetoids in group 3 have experienced subsides completely when they relax but tends to return when they are excited or embarrassed. Its appearance seems to be as automatic as the tachycardia which accompanies excitement and has not the appearance of a voluntary vice which holds the involuntary movements in check.

Opisthotonus.—Opisthotonus occurred in all cases in groups 1 and 2,

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and at some stage in their development in 18 of the 28 cases in group 3. The 11 who have never exhibited opisthotonus are the least handicapped physically and all are choreic.

Hypotonia.—Hypotonia was a feature of the disease in 21 of the 28 cases in group 3; in 10 cases the neck, trunk and limb musculature was hypotonic; in 8 the trunk and limb musculature alone appeared to be involved and in 3 the neck muscles only; in 1 case no reliable records are available. Of the 3 cases in which the neck muscles alone were hypotonic, 1 child is minimally handicapped physically and is choreic, while the other 2 are more severely handicapped and the "floppiness" of the neck muscles is associated with a rigidity of the limb muscles. Hypotonia first becomes evident at about the third month; in mild cases it persists for six months only, in the average case for twelve to eighteen months, but in severe cases for longer. 5 cases never exhibited any hypotonia, all are choreic and all are minimally handicapped physically.

Ataxia.—All the children who can walk, with 2 exceptions, have passed through an ataxic phase. The 2 children who were never ataxic sat up much sooner than any of the other children in this series, namely at 6 months, and they also learnt to walk correspondingly early, namely at 10 and 12 months respectively. The ataxia in the remaining children was naturally most conspicuous when they were learning to walk; it subsided gradually in the course of six months; it has not persisted permanently in any case.

Convulsions.—Convulsions are not infrequent in the severe cases of kernicterus, and occurred in 6 of the 10 cases in group 1, but they are uncommon in less affected cases. No cases have had repeated attacks of epilepsy; as Evans and Polani (1950) remark, kernicterus does not usually cause epilepsy.

Deafness.—The first case of deafness associated with kernicterus to be described was recorded by Coquet (1944), one of his 5 cases was both deaf and dumb; Lande (1948), next, noted that 4 of her 8 cases were deaf; Evans and Polani (1950), more recently, have observed deafness in 5 and possibly 6 children with kernicterus over the age of 1 year. Perceptive deafness is therefore a frequent concomitant of kernicterus. Perlstein (1950) suggests that it occurs in about 40 per cent of cases, Evans and Polani (1950) consider that the incidence is rather less, namely 20 per cent.

In my material there are 21 cases who are 5 years or more of age, and it has been possible to investigate the hearing adequately in 18 of these; of the remaining 3 who have not had a full audiometric examination 1 is too shy, a second too backward mentally and a third too handicapped physically to co-operate. 16 of the 18 cases have an appreciable perceptive deafness, 75 per cent of the children over 4, therefore, or more than 80 per cent of those tested, have a perceptive deafness. In 2 this hearing loss is complete, in 2 it is spread evenly through both the high and the

low frequencies, while in the remainder it affects mainly the high frequencies.

Deafness is so frequently found in association with kernicterus that the child's hearing should be investigated in every case, and this for three main reasons. First, any delay the child may experience in learning to talk may be ascribed to his physical handicap, i.e. to his choreo-athetosis and a contributing perceptive deafness may not even be suspected. Secondly, the child may be thought to be mentally retarded when he is in fact deaf. Thirdly, partial deafness is rarely suspected by the parents of this type of case; unless, therefore, the doctor takes upon himself the onus of investigating the child's hearing, the child may miss valuable years of appropriate tuition.

Intelligence.—Perhaps the most distressing feature of kernicterus is the associated mental impairment which is often present; the almost monotonous regularity with which cases are stated to be mentally retarded, and usually severely so, is disheartening. Yannet and Lieberman (1946) give the mental ages of 5 subjects with kernicterus aged 5, 7, 7, 18 and 19 years, as 5 months, 6 months, 3, 3, and 5 years respectively. Lande (1948) records the intelligence quotients of 6 of her cases as follows:

	Age in years	*I.Q.*	*Age in years*	*I.Q.*
Case 1 ..	$2\frac{1}{2}$	42	11	22
„ 2 ..	—	—	4	12
„ 3 ..	1	31	4	10
„ 4 ..	$1\frac{1}{2}$	25	4	17
„ 6 ..	$\frac{3}{4}$	44	3	19
„ 8 ..	—	—	4	18

All 6 are mentally deficient; and 4 became more so as they grew older. Lande's cases were drawn from an institution and therefore may not be typical of cases of kernicterus as a whole; moreover, she admits that the intelligence quotients of Cases 4 and 8 may be greater than the figures given suggest, and that the examiner did not realize that Case 8 was deaf. Dereymaeker (1949) states that kernicterus is always associated with mental retardation which often approaches idiocy; Agassiz *et al.* (1949), discussing the early diagnosis of cerebral palsy, state that, in the few cases due to Rh iso-immunization which they had encountered, mental retardation was so great that it was not possible to treat the physical handicap. However, both Pentschew (1948) and Evans and Polani (1950) suggest that mental impairment is not inevitable; the latter state that 1 of their cases is able to attend an ordinary school, while a second, who attends a school for the physically handicapped, has more than average ability, and a third is unusually intelligent.

Intelligence is probably not a function of any one part of the brain, but depends on the integrative action of the whole; it is independent of sight and hearing and motor function, in that the blind, the deaf and the crippled may still be intelligent; but its assessment is made difficult if

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either sight or hearing are impaired, or if muscular control is incomplete. Deafness, either partial or complete, and involuntary movements, are so frequently associated in cases of kernicterus, that it is easier to assume such cases are mentally retarded than to prove they are not.

In the attempt to assess the level of intelligence in these cases, use has been made of Terman-Merrill and Drever-Collins tests and of the progressive matrices; Terman-Merrill tests do not give a true guide to the level of the intelligence if the subject has an appreciable hearing loss; for such children the Drever-Collins tests are more applicable; these, however, though not dependent on speech or hearing, require that the child should have adequate control over his movements. Neither group of tests is of any value in the most severely handicapped cases and I have, in such instances, employed the progressive matrices. I am indebted to Mrs. F. E. Schonell, recently a research scholar in the Department of Pædiatrics and Child Health at the University of Birmingham, and to Miss Levy, a teacher at the Royal School for the Deaf, Birmingham, for their help in trying to reach a true assessment of the intelligence of the cases of kernicterus in my material; both agree that it is not possible to give an accurate assessment until the child has reached the age of 4 years; sometimes, if the child's physical handicap is very disabling, one must wait longer. For this reason I do not consider Lande's (1948) suggestion that mental retardation is progressive can be substantiated on her material.

Bearing in mind that Terman-Merrill tests tend to underestimate the level of the intelligence if hearing is impaired, 15 of the 21 cases of kernicterus are probably educable, with an intelligence quotient of 70 or over; 5 are feeble-minded, 1 only is an idiot. 5 (Cases 7, 10, 12, 13 and 18) have attended or are attending schools for the deaf; 2 (Cases 5 and 15) are at schools for the physically handicapped; 3 (Cases 3, 8 and 19) are attending ordinary schools; 1 child (Case 17) is in an institution. Case 18 was, until recently, attending a school for backward children and, although Terman-Merrill tests suggested that she was mentally retarded, she was sufficiently intelligent to realize that her school mates were backward. As she has an appreciable perceptive deafness I felt that Terman-Merrill tests did not give a true index of the level of her intelligence; Drever-Collins tests revealed an intelligence quotient of 110.

5 are 20 years old or more, 3 of these are too handicapped physically to undertake remunerative work but 2 are not so severely handicapped and both are earning their own living; the former in the upholstery department of a factory, the latter as an usherette in a cinema, both take care of their own money and the usherette actually supports her mother, for her father died recently.

Yannet and Lieberman (1944) and Snyder, Schonfeld and Offerman (1945) have suggested that Rh incompatibility may be associated with mental retardation in the absence of any damage to the basal ganglia.

Our findings are given in Table III.

TABLE III

Case	Age	Degree of kernicterus	Group	Hearing	Intelligence Quotient Terman-Merrill	Drever-Collins	Progressive matrices	Parental assessment
1	20	Severe	2	Impaired	—	—	Average	Average
2	20	Severe	2	Impaired	—	—	Average	Average
3	6	Mild	3	Impaired	—	—	—	Average
4	5	Moderate	3	Impaired	84	—	—	—
5	5	Mild	3	Impaired	100	—	—	—
6	10	Mild	3	Impaired	100	100	—	—
7	5	Mild	3	Deaf	—	—	—	Average
8	9	Mild	3	Impaired	98	—	—	—
9	11	Mild	3	Normal	33	—	—	—
10	13	Moderate	3	Impaired	50+	75	—	—
11	5	Mild	3	Cannot be assessed	Idiot	—	—	Idiot
12	24	Moderate	3	Deaf	—	—	Feeble minded	Dull
13	21	Mild	3	Impaired	—	—	Feeble minded	Average
14	23	Mild	3	Normal	85	—	—	Average
15	12	Moderate	3	Impaired	63	—	Above Average	Average
16	11	Mild	3	Impaired	40	—	—	Dull
17	16	Mild	3	Impaired	39	—	—	Dull
18	11	Mild	3	Impaired	60	110	—	Average
19	7	Mild	3	Impaired	70	—	—	Average
20	$5\frac{1}{2}$	Mild	3	Impaired	77	87	—	Average
21	4	Mild	3	Impaired	71	—	—	Average

Table III above gives details of the level of intelligence in cases of kernicterus, in so far as this has been ascertained, in relation to the child's powers of hearing and the degree of the kernicterus. For descriptive purposes the severe cases of kernicterus are those which exhibit, for the most part, dystonic movements, the moderate choreo-athetoid and the mild choreic movements only.

Case 3 is attending an ordinary school; his teachers are satisfied with his progress.

Case 7 and three other cases of kernicterus, who are not included in the above table but who are also attending schools for the deaf, are considered, by their teachers, to be of average intelligence.

More recently Gerver and Day (1950) have compared the level of the intelligence in 68 cases of icterus gravis, unassociated with kernicterus, with the level of the intelligence in 68 unaffected siblings. The average intelligence quotient of the former they found to be 102·7 and of the latter 114·5; the Stanford Binet scale was used; Gerver and Day consider that icterus gravis alone may cause a reduction in the intelligence quotient. Doubt has been thrown on Yannet and Lieberman's conclusions both by Cappell (1947) and by Race (1946). Cappell states, moreover, that in a series of about two hundred mothers, with mentally defective

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children, no reason was found to incriminate Rh incompatibility and he considered it improbable that Rh incompatibility could cause mental deficiency in the absence of overt hæmolytic disease in the infant. Creak (1947) also considers that mental retardation is closely related to the extent of the neurological damage, i.e. to the extent of the kernicterus. Gilmour (1950) has investigated the Rh groups of the mothers of 427 mental defectives and has concluded that Rh incompatibility, unless associated with erythroblastosis and kernicterus, plays no part in the production of mental deficiency. Yannet's (1950) latest pronouncement is that when mental deficiency is due to iso-immunization it is usually associated with choreo-athetosis but that mental retardation alone may also result from maternal Rh iso-immunization. Parsons (1947) also believes that mental deficiency may occasionally be the only sequel of hæmolytic disease of the newborn. This, however, would appear to be unlikely, for in following up uncomplicated cases of icterus gravis I have only come across one child who could be considered mentally retarded, and he had an intelligence quotient of 82. In any large series both backward and bright children will be encountered and occasionally mental retardation will be associated with, but I do not think caused by, simple icterus gravis.

My findings suggest that children with kernicterus tend to be mentally retarded, but they also indicate that mental retardation is by no means invariable or inevitable, and before an attempt is made to assess the level of the intelligence in a child with kernicterus care must be taken to determine to what extent the hearing is also affected.

Prognosis.—Before closing this description of the clinical types and stages of kernicterus, it may be asked if it is possible to foretell, at an early stage of the disease, its ultimate outcome. It is dangerous to generalize from these few cases, but it seems that the more dramatic the clinical onset of kernicterus the greater the final disability; the early development of generalized rigidity is also of grave prognostic significance and, if associated with thermal instability, death in infancy is inevitable. The development of a shrill, or cerebral cry often accompanies the onset of kernicterus in the more severely affected cases, but bouts of screaming and crying may persist until the infant is 1 to 3 years old, even in mildly affected cases. Opisthotonus is closely related—in cases of kernicterus—to athetosis; children who never exhibit opisthotonus develop chorea, though some cases who are ultimately choreic may exhibit intermittent, though never persistent, opisthotonus in infancy. Only in the least affected cases is there never any hypotonia.

(4) Correlation of Clinical and Pathological Findings

An attempt to correlate the clinical features of kernicterus with its neuropathology is a somewhat speculative enterprise.

It is easy to understand and explain why some cases die within a

week or two of delivery for there is an abundance of pathological material to guide us, both our own and published by others, more than 100 cases having been recorded; there is not, however, a similar abundance of pathological material on which to base an analysis of the symptomatology of the late cases of kernicterus. Moreover, any attempt to correlate the clinical picture of kernicterus as seen in cases surviving the neonatal period must take into consideration not only the involuntary movements exhibited by these subjects, but also the overtone of rigidity which is often present, as well as the emotional instability, the variable degree of mental impairment and the frequent association of perceptive deafness.

The extent of the pathological lesions in the acute phase of kernicterus.—In the experience of Baar (1952) based on necropsy findings of more than 50 cases of kernicterus, the areas most commonly pigmented, and damaged, are the hippocampus, nucleus subthalamicus, putamen, globus pallidus, caudate nucleus, the nuclear masses in the floor of the fourth ventricle, the inferior olives and dentate nucleus of the cerebellum and the vermis and flocculus. This is in close agreement with Becker and Vogel (1948), Dereymaeker (1949) and Claireaux (1950). Death, when it occurs, is nearly always due to the extension of the disease to the vital medullary centres, occasionally it is due to an associated intracranial hæmorrhage.

The extent of the pathological lesions in the chronic phase of kernicterus.—If the infant survives the acute phase of the disease and dies at a later date one might anticipate that the areas most commonly damaged in the acute phase would show the greatest cell loss at a later date. This is indeed the case, and in Table IV are summarized the findings recorded in late cases of kernicterus by Zimmerman and Yannet (1935) 1 case, Biemond and van Creveld (1937) 2 cases, van Westrienen and de Lange (1937) 1 case, FitzGerald, Greenfield and Kounine (1939) 2 cases, Sobel and Zucker (1940) 1 case, van Bogaert (1947) 1 case, and Claireaux (1950) 2 cases. The findings in 1 additional case are also given.

Chorea, athetosis and dystonia.—The involuntary movements exhibited by cases of kernicterus surviving the neonatal period range from the choreic, in the less affected cases, through the choreo-athetoid and athetoid to the dystonic; in the most severely affected group a generalized rigidity with opisthotonus is the presenting feature. The involuntary movements are accentuated by emotion and by volitional action; the movements are involuntary in that they are not willed, but they accompany willed action. It is probable that the movements are sometimes spontaneous, occurring independently of willed movements, for one of the more intelligent children once said to her mother: "My hands keep moving; I cannot keep them still." This would suggest that the involuntary movements associated with kernicterus may, in this respect, have an affinity with the spontaneous movements of ballismus, but they are never so wild or so violent.

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TABLE IV

	1	2 (*a*)	2 (*b*)	3	4 (*a*)	4 (*b*)	5	6	7 (*a*)	7 (*b*)	8
Cornu ammonis	+				+	+		N		+	+
Fascia dentata	+				+	+		N	+	+	+
Globus pallidus	+	+	+	+	+	+	+	+	+	+	+
Putamen	+	S	N	+	?S	+	+	?S	S	+	S
Caudate nucleus	+	N	N	+				?S			
Nucleus subthalamicus	+	+	+	+	+	+	+	+			
Thalamus	+							N			N
Red nucleus	+			N	N	N		N			+
Substantia nigra	+	N		N	N	N		N			N
Inferior olive	N			N	N	N		N			N
Dentate nucleus	+			N	N	N		N			S
Fornix		+	+								
Age at death	3 yrs.	3 mos.	4 mos.	1 yr.	4½ mos.	1 yr.	41 mos.	6 yrs.	4 mos.	17 mos.	12 mos.

Regions of the brain in which pathological lesions have been noted in late cases of kernicterus. +, marked loss of nerve cells. S, slight loss of nerve cells. N, normal content of nerve cells. 1, Zimmerman and Yannet. 2 (*a*) and 2 (*b*), Biemond and van Creveld. 3, van Westrienen and de Lange. 4 (*a*) and 4 (*b*), FitzGerald, Greenfield and Kounine. 5, Sobel and Zucker. 6, van Bogaert. 7 (*a*) and 7 (*b*), Claireaux. 8, Birmingham.

That chorea, athetosis and dystonia are closely related is well known. Kinnier Wilson (1940) states that torsion spasm is only a variety of athetosis, proximal rather than distal, and (1928) that athetosis differs from chorea only in that the movements in the former are slow and confluent, while in the latter they are discrete and rapid. Hunt (1917) regarded athetosis as a choreiform tendency with a moderate degree of rigidity and Wechsler (1938) that chorea is a rapid but less ample form of dystonia while dystonia is an amplified, slow movement of chorea. Athetosis might well be described as "dystonic chorea," though Gowers' (1906) original term "tetanoid chorea" is much more colourful. The transition from chorea through athetosis to dystonia would appear, therefore, to be due to the addition of an increasing element of rigidity; the latter reduces the speed and jerkiness of the choreic movements so that they become slower and more sinuous, in a word, more athetoid; athetosis is akin to chorea in slow motion. With a further increment of rigidity there is an increase in tension and the subject becomes what many physiotherapists call a "tension athetoid." The tension, according to Phelps (1941) is acquired; it is as though the child had learnt, consciously or unconsciously, that by tightening his muscles the involuntary movements could be held in check. Such a theory is attractive but it ignores the gradual increase of rigidity, organic in origin, which is apparent in the transition from chorea through athetosis to dystonia; in the latter the rigidity is maximal. Evans and Polani (1950) agree in considering that the rigidity, in cases of kernicterus, is an integral part of the disorder, and that it is not added subsequently by the patient. Herz

(1944) has also emphasized the influence of rigidity on chorea; choreic movements, he suggests, are due to an excess of motion without remarkable excess of tension, athetoid movements to an equal admixture of excess motion and excess tension, while in dystonia the excess tension is still more pronounced and it prevails over the excess of motion.

In their pure forms chorea, athetosis and dystonia, though bearing a close resemblance to each other, are distinct. In many cases of kernicterus, however, the distinction is difficult to make, and a child who, at rest, would appear to be choreic, when emotionally disturbed becomes choreo-athetoid or even athetoid; an athetoid in similar circumstances develops torsion spasm. Moreover there is a tendency, in some cases, for the involuntary movements to become less prominent as the child grows up; the athetoid becomes choreo-athetoid and the choreo-athetoid choreic. That this improvement is an integral part of the disorder was noted by Pentschew (1948); that it occurs is not surprising in the light of Kennard's (1944) experimental work.

I have emphasized the close association of the involuntary with the voluntary or willed movements. Kinnier Wilson (1940) drew attention to this and noted that the spasms of dystonia were intensified by and constantly interfered with willed movements. Horsley (1890), many years previously, had stated that he regarded athetosis as a form of cortical discharge; on these grounds he removed the "thumb area" from a case in which athetoid movements had started in the thumb; the athetosis subsided for two weeks. He later (1908) operated on a boy of 14 who, from the age of 7, had gradually developed athetoid movements of the left hand followed by convulsive movements of the whole of the left arm; stimulation of the right precentral gyrus gave rise to a repetition of these movements; this area was therefore removed and the athetosis subsided completely; the limb remained flaccid for twelve days, but thereafter some power returned and the arm could be used, for example, when dressing. Bucy and Buchanan (1932) and Bucy (1942), by following this line of treatment, have also demonstrated, on numerous occasions, the dependence of athetosis on cortical impulses. This dependence of athetosis, choreo-athetosis and chorea upon an intact and fully developed corticospinal system explains why the involuntary movements in kernicterus do not arise at the onset of the disorder, but make their appearance only when the pyramidal and extrapyramidal systems are physiologically mature; myelination is not complete until the age of 2 years, according to Lassek (1948). As the normal child grows the first muscles to come under voluntary control, apart possibly from those concerned with sucking—and sucking appears to be automatic rather than voluntary in a baby—are the extrinsic muscles of the eye. The athetoid syndrome should, therefore, first become manifest in the movements of the eyes, and this is indeed the case, for the rolling movements of the eyes in which the pupils are buried behind the lower or upper lids, seen

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from earliest infancy, are as closely related to athetosis as is nystagmus to intention tremor. As the child grows and begins to use first his hands and then his arms and legs the involuntary movements appear in these also. With further growth and development, and particularly if a modicum of emotional control is achieved, the voluntary control of the child increases; this improvement is first made manifest in the control of the extrinsic ocular muscles and the bizarre rolling movements of the eyes subside. Perlstein (1950) has said that often cases of kernicterus cannot turn their eyes up or down, usually due to a supranuclear lesion, but in only 2 of the cases I have seen have the ocular movements been limited; 1 child cannot raise the eyes above the horizontal, another has a bilateral external rectus palsy.

The involuntary movements in kernicterus almost certainly develop as a result of the lesions in the corpus striatum, globus pallidus and nucleus subthalamicus, for athetosis has been shown to follow lesions in the caudate nucleus and putamen (Alexander, 1942), globus pallidus (Papez *et al.*, 1938) as well as in the ventrolateral nucleus of the thalamus (Schuster, 1937). That a syndrome analogous to ballismus does not occur in kernicterus, although the nucleus subthalamicus is so constantly affected, is probably due, as FitzGerald, Greenfield and Kounine (1939) suggest, to the concomitant involvement of the basal ganglia; in addition, the lesion in the nucleus subthalamicus may, in the less affected cases, be incomplete. Damage to the globus pallidus, according to Davison (1942), is essential for the production of rigidity, and the degree to which this ganglion is affected in kernicterus may determine the extent to which the choreic foundation is modified by rigidity. If the globus pallidus is virtually completely destroyed rigidity is maximal, as in the most severely affected cases of kernicterus. It would appear, then, that the varying grades of involuntary movement, ranging from the choreic to the dystonic, seen in cases of kernicterus depend to a great extent on the proportion of cells surviving in the nucleus subthalamicus and in the globus pallidus. If the lesion is confined to the former and is partial the subject is choreic; with increasing involvement of the globus pallidus, from which the nucleus subthalamicus receives many afferent fibres, there is a corresponding increment of rigidity with the emergence of athetosis and dystonia.

Rigidity.—In the most severely affected cases of kernicterus a generalized and remarkable rigidity develops at an early age. It is associated with head retraction and opisthotonus; the legs are fully extended, the arms are usually adducted at the shoulders and flexed at the elbows, and the fists are clenched firmly. The position assumed by these cases differs only from that of decerebrate rigidity as described by Sherrington (1898) in the monkey in that, in the monkey, the "arms" are thrust backward at the shoulder-joint and extended at the elbow, but it is exactly analogous to the decorticate state in *Macacus rhesus* as described by Magnus (1926).

The rigidity, too, is of the same plastic type. In two severely affected cases of kernicterus who are still alive it is possible to demonstrate the positive supporting or "magnet" reaction, though not the tonic neck reflexes, for the torsion spasm effectively prevented any attempt to rotate the head.

Ataxia and hypotonia.—Lande (1948), Evans (1948), Pentschew (1948) and Evans and Polani (1950) have drawn attention to the ataxia and hypotonia which characterize many cases of kernicterus; Lande (1948) has even suggested that, though some cases present with generalized athetosis and others with persistent rigidity, a third group are primarily ataxic and a fourth atonic. Pentschew (1948) and Evans and Polani (1950) consider that the hypotonia exhibited by many of the cases is a transitory phenomenon and that the disease follows a pattern, presenting with different signs and symptoms at different ages. This conception is confirmed by a study of the case histories in my material. Hypotonicity of the neck and/or limbs and trunk musculature was observed at one time or another in all except 14 of the 41 cases in my series; it was not noted only in 5 minimally handicapped physically and in 9 who, at an early age, developed a generalized spasticity. Hypotonicity was present at one time or another in all the intermediate grades; in these it is usual for the infant, after the initial onset of kernicterus between the third and eighth days of life, to improve and sometimes to appear to be clinically normal, but within the next two or three months hypotonicity of the neck and/or limb and trunk musculature becomes apparent. This hypotonicity may be so marked that the infant lies almost motionless for hours at a time; one mother was able to leave her baby lying unattended on the kitchen table while she did her household duties, because she knew the baby would not move. The hypotonia of the neck muscles is most evident when the infant is lifted, for the head then falls lifelessly back; the mother often confesses that when she lifts her baby up she has to support the head firmly as she is afraid it may fall off. Sooner or later jerky, twitching movements gradually make their appearance, tone returns to the muscles and the child can usually sit up by the time he is 18 months old, though exceptionally he may not even be able to hold his head up until he is 5 or 6 years old. At 2 years of age he begins to learn to stand and it is immediately apparent that the movements of his limbs are jerky and that he has little sense of balance. He clings tenaciously to the furniture for support and, when he plucks up courage to sally forth by himself, he totters or staggers across the room on a broad base, tumbling frequently. I wondered, at first, if this instability might not be caused by the associated involuntary movements, but I do not think this can be so, for the involuntary movements persist long after the child has learnt to stand, to walk and even to run without falling. The instability is, I think, primarily a disturbance of equilibrium, it is not associated with nystagmus, nor have I been able to demonstrate any evidence of

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intention tremor in these children, though the movements of their limbs are jerky. The clinical picture presented by these children simulates, in some respects, the early stages of the mid-line cerebellar tumour syndrome in children. Dow (1938*a*, *b*) has shown that, in cats, dogs, monkeys and chimpanzees the removal of the nodulus is followed by a disturbance of equilibrium without a trace of tremor. The description he gives (1938*a*) of his monkeys immediately after the removal of the nodulus could well be applied to many cases of kernicterus at this stage of their disorder. The surface of the flocculo-nodular lobe is not infrequently, in cases of kernicterus coming to autopsy during the acute phase of the disease, stained a bright golden yellow; it is the only part of the cerebellar cortex in Baar's (1952) experience, to be picked out in this characteristic fashion. The flocculo-nodular lobe is the oldest part, phylogenetically, of the cerebellum; it develops as a direct outgrowth of the vestibular nuclei, and it may well be that the disturbance of equilibrium experienced by cases of kernicterus is due to involvement of this part of the cerebellum or of its connexions with the fastigial nucleus and nuclei of Deiters or Bechterew. Nerve cells in the dentate nucleus and inferior olive are also commonly damaged in kernicterus and this, too, probably contributes to the ataxia. In the experimental monkeys mentioned above, the ataxia does not persist for more than two months; it lasts longer in the developing child probably because he is learning to balance for the first time; the child is further handicapped by involuntary movements.

The hypotonia exhibited by these subjects is usually most conspicuous in the neck muscles, but in some cases the tone of the neck muscles appears to be within normal limits and the trunk and limb musculature only are hypotonic. The hypotonia cannot be due to any intrinsic muscle weakness, for in the neck, for example, the muscles which appear to be the weakest are the very muscles which contract most forcibly to produce intermittent head retraction. It is possible that the hypotonia is associated with cell loss in the inferior olive and dentate nucleus of the cerebellum, but I think it is probably associated with partial lesions of the vestibular nuclei; these have been observed in the acute phase of the condition both by Bertrand (1946) and by Dereymaeker (1949) and also by the writer. The vestibular nuclei share with the cochlear nuclei a susceptibility to damage not shared to a similar degree by the other cranial nerve nuclei, and the importance of the tonic labyrinthine reflexes in the maintenance of normal muscle tone, not only in the neck but also in the trunk musculature, has been amply demonstrated by Magnus and de Klejn (1912) and Magnus (1926).

The hippocampus and emotional control.—One of the outstanding features of most children with kernicterus is their emotional instability; they are easily frightened, easily reduced to tears and withal easily delighted; they have great difficulty in hiding their feelings, and grief and joy quickly find expression. The mothers of many of the cases of kernicterus

were reluctant, and one actually felt unable, to bring their children to hospital for examination and investigation because of the mental distress it would cause; considerable patience was needed both to win the child's confidence and, having won it, to maintain it. I suspected, at first, that this fearful attitude on the part of the child might be an aftermath of frequent heel pricks and other trauma received in hospital in infancy and that the child had consequently developed a fear of hospitals and doctors; no doubt this has played a part, but in other children whose early lives were subjected to similar trauma but who are neurologically sound no such emotional instability persists. Moreover, 8 of the cases of kernicterus had never been conditioned in this way, but they also lack emotional control. It might be suggested that the child's volatile temperament is conditioned by his physical disability, but children—in my experience—with other forms of cerebral palsy, e.g. a hemiplegia or paraplegia, do not commonly exhibit a comparable lack of emotional control. I think, therefore, that this lack of emotional control shown by many cases of kernicterus is organic in origin.

In cases of kernicterus any emotion accentuates the involuntary movements; the reverse is also true, that with repose and relaxation they subside. It is a common experience that a strong emotion adds strength to any given action; a blow in anger, for example, is more violent though not necessarily more accurate than a premeditated blow, and Murphy and Gellhorn (1945) have shown experimentally in the cat and monkey that stimulation of the hypothalamus greatly increases the response from cortical stimulation. The only precise movements ever carried out by one of the more severely handicapped cases in my series has been the sudden seizure of a forbidden kettle or carving knife which is carried out with the precision of a hawk and in response to an irresistible urge. Carlson (1941), who is himself afflicted with involuntary movements of an athetoid character, describes how his hand once swooped suddenly on an apple; he was being driven in a wagon at the time and he saw some apples in the front of a fruit stall; before he was aware of what had happened his hand had seized one. This was the first time, he said, that his hand had ever done his bidding, though the bidding seems to have been largely subconscious. Such automatic responses to strong emotion no doubt play an important part in the lives of lesser creatures, but man is able to hold himself in check, and when he has a sudden almost uncontrollable impulse to action he is able to count ten and think again; this the case of kernicterus cannot do.

Ever since Hughlings Jackson and Beevor (1890) recorded the association, in epileptic, of fits associated with a "very horrible smell" and a tumour occupying the right temporo-sphenoidal region and amygdalæ, the hippocampus has, until recently, been thought to be concerned with smell. Allen, however (1940, 1941), has shown that bilateral extirpation of the hippocampi, in dogs, has little if any effect on conditioned reflexes based on responses to smells, and that removal of the pyriform-amygdaloid areas did not prevent dogs picking out a packet containing

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meat from three other packets of like size and texture. Le Gros Clark and Meyer (1947) were unable to trace any fibres, in the rabbit, from the olfactory tract to the entorhinal area of the hippocampus, and Brodal (1947), in an extensive and comprehensive review of the functions of the hippocampus, concluded that its association with smell was not proven. Morphologically the hippocampus, with its dense layer of pyramidal cells, has an effectory structure; moreover man, a microsmatic mammal, possesses a very large hippocampus, relatively and absolutely the largest hippocampus in relation to the olfactory bulb of all mammalian species. Brodal (1947) considered that this region may, possibly, be related to autonomic function and more particularly to the emotional changes. Papez (1937) had originally suggested that the hippocampus might be concerned with the emotions; he proposed that the hippocampus, hypothalamus, anterior thalamic nuclei, and gyrus cinguli with their interconnexions constituted a harmonious mechanism which elaborated the functions of central emotion, as well as participated in emotional expression. In kernicterus, in both the acute and chronic phases, the hippocampus is almost constantly affected; it is possible that the great poverty of emotional control exhibited by these subjects is related to this lesion. In no case was there any loss of olfaction or inability to discriminate between pleasant and unpleasant smells.

Deafness.—Three-quarters of the cases of kernicterus in my series who are over the age of 4 years have a perceptive deafness; in most the loss is greatest in the high frequencies; in nearly all cases this loss affects the hearing of both ears equally. By definition the deafness is associated with lesions either of the cochlea or of its central connexions, and it is the receptors or the neurones transmitting the higher frequencies which are most constantly affected. My studies (Crabtree and Gerrard, 1950; and Gerrard, 1952) suggest that the deafness is due to cell destruction in the cochlear nuclei. This cell destruction has also been observed by Dublin (1951). I have, however, only been able to examine fully the cochlea and its central connexions in 2 cases which died during the acute phase of kernicterus, the cochlear nuclei have been examined both macroscopically and microscopically in many more instances. No material from a child with kernicterus, and known to have been deaf, has yet been examined, so it has not been possible to correlate the extent of the hearing loss with the lesions in the central nervous system.

Lesions of the cochlear nuclei have been noted by a number of authors (Beneke, 1907; Esch, 1908; Bertrand, 1946; Potter, 1947; and Dereymaeker, 1949). Many more have noted icteric pigmentation in the floor of the fourth ventricle; this pigmentation is always most conspicuous near the surface, apart from the inferior olive, and if pigmentation is indicative of cell damage, and there are good reasons for believing this to be so, then it is not surprising that neurones in the dorsal cochlear nuclei, transmitting the higher frequencies, are more constantly affected than those transmitting the low frequencies.

Temperature regulation.—Thermal instability is by no means a constant feature of kernicterus but occasionally, among those who are most severely affected and who also survive the neonatal period, the temperature runs a high and irregular course. 4 of the cases in my series ran a high fever, often between 105° F. and 107° F., in the presence of minimal infection;

Zimmerman and Yannet's (1933 and 1935) also experienced episodes of high fever, as did van Westrienen's (1935 and 1936); all these died at an early age. In van Westrienen's case the temperature vacillated between 36·5° C. and 41·6° C. for three months; Zimmerman and Yannet's case often ran a temperature of over 104° F. in the absence of any significant infection, and blood cultures were always sterile. I have noticed also that there is, not infrequently, a transient rise of temperature, for example to 100° F., at the onset of kernicterus in those who have survived, but the temperature in many normal infants is not very stable at this time, so no undue significance can be ascribed to this; 1 case which died during the neonatal period also had a marked terminal pyrexia. I have not, in cases surviving the neonatal period, seen any children who have persistently run a subnormal temperature, but in 2 cases which died and in 1 which is still alive, infancy was marked by frequent bouts of profuse perspiration in the absence of any fever or external heat; 1 infant perspired so freely that the cot blankets had to be changed several times a day.

Ranson *et al.* (1937) have demonstrated that lesions of the anterior hypothalamus (paraventricular, supra-optic and lateral hypothalamic nuclei) in monkeys, result in an inability to lose heat; if the monkeys are placed in a hot room their temperatures rise to a dangerously high level. Zimmerman and Yannet (1935) related the hyperthermia in their case to a lesion in the mammillo-infundibular nucleus of the hypothalamus. Lesions of the posterior hypothalamus, according to Ranson *et al.* (1937), result in an inability to regulate against cold, and though none of my cases exhibited any hypothermia, excessive heat loss may well have been associated with the excessive perspiration which occurred in 3 cases; the temperature may have been kept within normal limits by the careful nursing they were given. Lesions of the hypothalamus are not common, according to Dereymaeker (1949) and this, no doubt, explains the infrequency of thermal instability in cases of kernicterus.

Conclusion

The above attempt to correlate the clinical manifestations of kernicterus with its neuropathology is, of necessity, both tentative and incomplete. Knowledge of the anatomy of the brain has always outstripped knowledge of its physiology, and attempts to analyse the contribution of different parts of the brain to both voluntary and involuntary movements is not without danger, for the integrative action of the nervous system is such, as Walshe (1947) has reaffirmed, that the whole works in unison. The pyramidal and extrapyramidal tracts are alike essential to all willed movements, whether discrete or stereotyped; these tracts, Denny-Brown (1950) suggests, contribute complementary features to willed movements, and integration occurs both at cortical and at subcortical levels; he postulates that it is a lack of integration, at progressively lower levels, which leads to the development of chorea, athetosis, dystonia and parkinsonian tremor.

(5) Appendix

Kernicterus associated with Rh iso-immunization.

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Case A, an example of the type of case in group 1.
Case B, an example of the type of case in group 2.
Case C, an example of the type of case in group 3.

Kernicterus not associated with Rh iso-immunization.
Case D.

Case A.—Wendy B., aged 10 months at death.

Family history and blood groups: Father O Rh positive. Mother A Rh negative. In December 1946 the serum contained anti D acting in saline and in albumin. She has never received any blood transfusions.

First pregnancy 4.8.34, male, full term (hereafter F.T.), breech delivery, birth-weight (hereafter B.W.) 10½ lb.. never jaundiced or anæmic, O Rh positive.

Second pregnancy 10.6.36, female, F.T., normal delivery (hereafter N.D.), B.W. 9 lb., never jaundiced or anæmic, O Rh positive.

Third pregnancy 1938, miscarriage at 22 weeks.

Fourth pregnancy 1939, miscarriage at 10 weeks.

Fifth pregnancy 25.12.40, male, F.T., N.D., B.W. 8¾ lb. never jaundiced or anæmic, O Rh positive.

Sixth pregnancy 31.1.42, female, F.T., N.D., B.W. 8½ lb., never jaundiced or anæmic, O Rh positive.

Seventh pregnancy 22.3.44, female, F.T., N.D., B.W. 8½ lb., never jaundiced or anæmic, O Rh positive.

Eighth pregnancy 16.4.45, female, F.T., N.D., B.W. 8½ lb., icterus gravis, transfused, now alive and well, A Rh positive.

Ninth pregnancy 25.12.46, male, F.T., N.D., B.W. 9 lb. 1 oz., icterus gravis, transfused, now alive and well, O Rh positive.

Tenth pregnancy 26.2.48, Wendy. Gestation 37 weeks, N.D., B.W. 7 lb. 4 oz., kernicterus, O Rh positive.

Jaundice became apparent three hours after delivery, deepened quickly and cleared after fifty-six days. At birth her general condition was good, she took feeds well from the breast and appeared to be quite lively until midnight on the fourth day of life, when she suddenly refused feeds. During the next three days she was irritable and had a cerebral cry, but then improved and once again sucked eagerly. On the ninth day of life the hæmoglobin had fallen to 76 per cent. She was given a transfusion of O Rh negative blood and some nineteen days later a further transfusion. On the twenty-fourth day of life the stools were acholic.

At 7 weeks of age she took little or no notice of her surroundings, her eyes would not follow a light, though the pupils reacted briskly to light and the fundi were normal. She was inclined to vomit. Three weeks later she had become a restless baby; the arms were never still; she would put her tongue in and out time and time again, hour after hour. She vomited daily; the vomitus was usually a small regurgitation but occasionally it was projectile; it was not sufficiently large to prevent weight gain. She smiled first at 16 weeks of age. At 6 months of age she still would not look at her bottle, when feeding, and her eyes frequently turned upwards, revealing a large band of sclera below the irises. The muscle tone of the limbs was usually normal but intermittently the muscles contracted and became stiff.

At 8½ months of age she was admitted to hospital because her mother had found it increasingly difficult to manage her. The limbs were now stiff, more so on the right than on the left side. She was unable to sit up and lay in her cot with her head thrown well back, and her mouth wide open. She screamed most of the time unless heavily sedated. She sucked vigorously.

During the next six weeks she ran an intermittent fever; the temperature varied

between 103° F. and 105° F. and the pulse and respiration rates rose correspondingly. She had a little infection of her upper respiratory tract but the fever was out of all proportion to the severity of the infection. The latter responded slowly to the exhibition of penicillin and sulphonamides. Terminally the temperature, pulse and respiration rates all rose in unison, mimicking closely the final stage of an untreated case of tuberculous meningitis. Autopsy confirmed the clinical impression that the fever was greater than could be accounted for by the infection.

Case B.—Dick J., aged 20 years 2 months.

Family history and blood groups: Father A Rh positive. Mother A Rh negative. In May 1948 the serum contained anti D acting in albumin but not in saline. She has never received any blood transfusions.

First pregnancy 1913, female, F.T., S.B., craniotomy after a long labour.

Second pregnancy 1916, male, F.T., N.D., jaundice developed on the second day of life; he had several convulsions and died on the fifth day.

Third pregnancy 1920, male, F.T., S.B., movements ceased two weeks before delivery.

Fourth pregnancy 1925, male, induced at 36 weeks, labour started forty-eight hours later; died while being delivered. He looked normal.

Fifth pregnancy 31.7.30, Dick. Cæsarian section at 36 weeks. B.W. 8 lb. 5½ oz., kernicterus, A Rh positive.

He was feeble at birth. On the following day he became drowsy and did not cry well. On the third day jaundice was obvious, it deepened rapidly and cleared after three weeks, revealing an anæmia. On the seventh day of life he collapsed and was given 10 c.c. of maternal serum intramuscularly. During the next three days he received a further 26 c.c. of maternal serum intramuscularly. He did not take feeds well from the breast and, though he took more readily from the bottle, he lost much weight and when 26 days old he was still 7½ oz. under his birth-weight.

At 5½ months his mother wrote: "He really is a fine boy" but he is "now rather cross cutting his first teeth." At ten months she added: "I am afraid I have not quite such good news of my little son. When I wrote a few months ago one did not notice him being backward, but he is now old enough to sit up in his pram yet is not able to do so." At 14 months his mother stated that he was: "Much better, though still unable to sit up without support. He has three teeth and wants to be on his feet all the time. He does not talk yet, except in saying 'dad' and 'mum'." When he was 8 years old his general practitioner wrote (not to the writer) saying: "When last seen, some months ago, the condition of the babe was so utterly lamentable that I felt you would wish you hadn't been so clever as to save it. A complete idiot and largely paralysed and the mother saying 'Isn't he coming on?' "

Later, in answer to leading questions, the mother stated that Dick J. was very floppy when a baby and that he lay motionless in his pram for long spells at a time, but at times he would become stiff and arch his back. The athetoid movements, she thought, had always been present to a greater or lesser degree.

At the time of writing he is still severely handicapped physically; he has never been able to sit up by himself, nor can he walk. He has to be dressed and carried round by his father, being too heavy for his mother and also too prone to shoot out an arm or a leg, without warning, which might well knock her over. Excitement accentuates the athetosis, resulting in grotesque and bizarre contortions. Sleep banishes it. "He lies so quietly when he is asleep," his mother said, "you would never know he was a spastic." Whenever he is completely absorbed in any activity he becomes, for a moment, still; but the more he tries to be motionless, the more violent the lashing of his limbs. On the other hand, should he suddenly see something which he knows he is not allowed to touch, e.g. a knife or kettle, his hand will swoop on the forbidden target with the precision of a hawk.

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Physical examination was difficult, for the excitement of being examined precipitated marked dystonic postures of the trunk and athetoid movements of all four limbs; the arms at one moment are adducted at the shoulders and flexed at the elbows, and at the next are fully abducted and extended. When he is seated in his chair the legs are adducted at the hips so that one knee rests on the other, the hips and knees are at one moment flexed and at the next partially extended, and resemble in some measure the movements of a knock-kneed racing cyclist. The torsion spasms of the trunk are to some extent controlled by the chair in which he is strapped but his head moves rapidly from side to side as he looks first over one shoulder and then over the other—rather like a spectator at a tennis match. The muscle tone of all the limbs is increased, the resistance to passive movements being steady in character and not cog-wheel or clasp-knife; the tendon-jerks are of normal intensity. The plantar responses are flexor; the abdominal reflexes are present. Sensation is normal. He experiences great difficulty in undertaking any co-ordinated movement, though he can, with much effort, nearly touch the examiner's hand, and when asked to touch his own nose he covers most of his face with his outstretched hand. The only voluntary movement he can readily make is to dig with a small trowel, which has to be tied to his hand or he would drop it. Eleven years ago he was able to walk, if supported, but during the war years his father did not have time to spare to help him and he can now no longer even attempt to walk. If he is supported he will stand on one leg with the other leg tucked under his buttock—"I stand like a stork," was his own picturesque comment. The movements of his eyes are full, there is no nystagmus; the ocular muscles are the muscles over which he has the most perfect control and his eyes will remain focused on a given object quite steadily until his head is suddenly switched through 90 or 180 degrees. Mastication is performed slowly but adequately and he has no difficulty in swallowing. Breathing is laboured, inspiration and expiration being excessive. Vision and olfaction are normal; the pupils respond both to light and on accommodation. It was not possible to examine the ocular fundi in any great detail, as he was unable to keep his head still, but I saw no abnormality in them. He has an appreciable perceptive deafness and his speech is indistinct, but this is probably due more to defective muscular control than to diminished auditory perception. Tested with the progressive matrices his score was in the upper limit of the average range; his intelligence is definitely not defective.

Case C.—Margaret P., aged 23 years 1 month.

Family history and blood groups: Father A Rh positive. Mother A Rh negative. In May 1946 no anomalous agglutinins or blocking antibodies were present in the serum. She was not anxious to be subjected to the Bessis test. She has never received any blood transfusions.

First pregnancy 9.9.11, female, F.T., forceps delivery, B.W. 7½ lb., never jaundiced or anæmic, A Rh negative.

Second pregnancy 22.10.21, male, F.T., N.D., B.W. 7½ lb., never jaundiced or anæmic, O Rh positive.

Third pregnancy 14.8.27, Margaret, F.T., N.D., B.W. 5½ lb., kernicterus, O Rh positive.

Jaundice was first noted at birth; it became deep and faded after eighty-four days. She never became anæmic. She was breast fed, and always sucked well. In infancy she was somewhat hypotonic but every now and then became stiff—as though stretching herself. She did not sit up until she was 18 months old; she walked alone six months later, but unsteadily at first, falling more than a normal toddler usually does. She did not begin to say simple words until she was 2½ years

old. Sentences came later but at 5½ years of age her speech was still indistinct. At this time choreiform movements were first noticed, her gait was ataxic and she was emotionally labile. Between the ages of 4 and 7 years she had several generalized convulsions but she has had none since and the choreiform movements have gradually diminished. At the age of 8½ years she started to attend a special school, where it was noted that she was "very nervy and shaky," while her movements and speech were both "jerky." She could read words of four and five letters, her writing was slow and uncontrolled, her drawing "very poor." A year later she could read well, her writing had become "quite good," and her general behaviour left little to be desired save that she was inclined to giggle a great deal. When she left school, aged 15 years, she could read fluently, speak clearly and write steadily. She had made a blouse and had embroidered a bag. She was a polite, quiet, painstaking pupil.

The next year she spent at home and then, aged 17, undertook her first job, assembling electric switches. She managed the delicate work easily but was soon told by the works' doctor to find a less exacting occupation. She then made sausages for a year but once more changed her work, this time at her mother's instigation, and became an usherette at a cinema. She was very reluctant to undertake this new occupation, feeling that she would be unable to manage the stairs, especially in the dark. Her fears, however, were ill grounded and she soon took them two at a time.

She is now 25 years old, physically well developed, taking a natural pride in being attractively dressed and very much averse to any suggestion that she is, in any way, abnormal. Her earnings—her father died recently—provide for both her mother and herself. "I would be lost without her," her mother volunteered. A casual observer would probably note nothing unusual about her, but she is exceptionally shy and is as easily upset as she is easily pleased. Her movements, when she is excited, tend to be choreic, the left arm being somewhat less steady than the right; she also grimaces a little.

Owing to her sensitive nature it was not possible to subject her to an adequate physical examination, but the knee-jerks were normal and equal and her co-ordination is good; her powers of smell were not tested but she seemed to enjoy applying a well-perfumed powder to her cheeks; the eye movements appeared to be full but the ocular fundi were not seen. Her hearing could not be assessed with the audiometer but is probably normal for her speech is clear and distinct and her vocabulary is good. Her intelligence quotient (Terman-Merrill) is 85.

Case D.—John N.

Family history and blood groups :Father O Rh positive, genotype R_1R_1 CDe/CDe. Mother O Rh positive, genotype R_2r cDE/cde. The serum contains no anomalous agglutinins either in saline or in albumin.

First pregnancy 1934, miscarriage at two months.

Second pregnancy 1935, John, gestation 36 weeks, forceps delivery, B.W. 5 lb., kernicterus, O Rh positive, genotype R_1R_2 CDe/cDE.

Third pregnancy 1936, female, B.W. 4 lb., died ten hours after delivery; death was due to prematurity (necropsy performed).

Fourth pregnancy 1946, female, Cæsarian section at 37 weeks, B.W. 6 lb. 1 oz., never jaundiced or anæmic, O Rh positive, genotype R_1R_2 CDe/cDE.

He became jaundiced on the first day of life, the jaundice deepened rapidly and persisted for more than three months. He never became noticeably pale. He first sat up at 3 years, started to talk at 4 and to walk at 4½. His movements are now athetoid, he has a high frequency perceptive deafness and his intelligence quotient is 60 (Terman-Merrill).

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Part II.—The Ætiology of Kernicterus

Attention has been drawn (p. 543) to the areas of the brain most commonly damaged and bile stained, and although it was stated that bile staining is most conspicuous in the hippocampus, nucleus subthalamicus and other nuclear masses, yet pigmentation is also often seen in the subcortical white matter and occasionally—apart from the hippocampus—in the cortical grey matter itself. Sometimes, as Schmorl (1903) noted in one of his cases, the whole brain is stained diffusely yellow and small lentil-sized areas of necrosis may be seen in the white matter. A comparable case has been observed in our material. Gilmour (1944) noted, in one of his cases, that the icteric staining of the brain was limited to the cerebral cortex. More commonly, however, the subcortical white matter is, on the whole, free from pigmentation; but, here and there, there are small areas, usually 2 to 5 mm. in diameter, where the white matter is stained yellow; these areas appear opaque and necrotic. Gilmour (1944) noted that, in 3 of 10 cases, icteric pigmentation in 1 case was in the centra-semiovalia, in another in the fronto-parietal region below the convolutions, and in the third was diffuse throughout the whole brain. Yellowish-white or white flecks of necrosis were also present in the cerebral white matter in 2 of these cases, and also in a third in which the cerebral white matter was free of pigment.

Beneke (1907) observed in his case that the whole brain was slightly icteric, while the hippocampus, nucleus subthalamicus and the nuclei of the fifth and eighth cranial nerves were deeply pigmented. He again noted, in Esch's (1908) case, that the whole brain was slightly icteric while the corpora striata, globus pallidus, nucleus subthalamicus and floor of the fourth ventricle, including the cochlear nuclei, were stained deep yellow. The cerebellum was also seen, on cross section, to be stained yellow. Yllpö (1918) also observed diffuse icterus of the brain associated with deeper staining of the nuclear masses. Comparable findings have not been infrequent in our experience. Bertrand (1946) noted pigmentation in the grey matter and underlying white matter of the orbital and lateral surfaces of the frontal cortex and in the subependymal region of the anterior horns of the lateral ventricle associated with nuclear jaundice. He emphasized the widespread nature of the disease. Dereymaeker (1949) concluded that not only the nuclear masses but also the cerebral cortex itself were almost constantly damaged. In 6 consecutive cases of kernicterus, dying in the acute phase, I observed discrete areas of pigmentation in the subcortical white matter in 5; this pigmentation was, in each case, adjacent to the anterior or posterior horns of the lateral ventricle, but in 1 case pigmentation was also present in the cortex of the lateral surface of the temporal lobe.

It would appear from the above that Groups I and II of Schmorl actually merge into one another. Cell destruction and pigmentation are most constant in the nuclear masses, but they are not confined to them. In

some of the late cases of kernicterus also, for example Burghaard and Schleussing's (1933) and Sobel and Zucker's (1940), the lesions are correspondingly widespread. I do not think that Schmorl's Groups I and II are different diseases; they are variants of the same syndrome.

The cytological changes seen in the acute phase of kernicterus have been the subject of numerous studies. Initially the cell nucleus becomes somewhat reduced in size, hyperchromatic and takes up basic dyes and hæmatoxylin with avidity, it is often a little eccentrically placed and may become fragmented; the cytoplasm is homogeneous and stains a uniform pink with eosin. This cell change is seen most characteristically in the hippocampus (Gilmour, 1944). The nucleus later disintegrates. The cytoplasm loses its affinity for acid dyes, it stains poorly and, before its complete dissolution, the cell outline or "ghost cell" may be all that is visible. In other instances the nucleus and surrounding cytoplasm both take up stains poorly, and the nuclear material appears gradually to fade away; on microscopical examination all that may be seen is a pool of unstained cytoplasm surrounded by the cell membrane. Bile staining may be observed both in apparently normal and also in disintegrating cells, as well as in the extracellular tissues. This staining is best seen in frozen sections. Glial infiltration succeeds necrosis. Perivascular cuffing is also occasionally observed. Compound granular cells are uncommon in our experience.

The nature of the pigmentation has been the subject of much speculation. Schmorl (1903) suggested that the pigment was not bilirubin because it fades on exposure and is not oxidized to biliverdin. Pickles (1949) has found an abnormal bilirubinoid pigment in the serum of 2 cases of kernicterus. I have also encountered a similar pigment in the cerebrospinal fluid of 2 cases of icterus gravis as well as in a case of kernicterus. Baar (1952), however, has noted, in 2 instances, that the pigmentation has become dark green in paraffin blocks, and in a third instance intracellular pigment has been observed, in frozen sections, to darken and become green with the lapse of time. Dereymaeker (1949) is satisfied that the pigment possesses the physical and chemical characteristics of bilirubin. Bilirubin is certainly present in excess in the circulation in cases of kernicterus and one would therefore not be surprised to find bilirubin in damaged cells.

Various suggestions have been put forward to explain the development of kernicterus; these can conveniently be divided into those put forward before the importance of iso-immunization in the production of hæmolytic disease of the newborn was known, and those which have been put forward subsequently. Beneke (1907) suggested that the nerve damage was due to a toxin, trauma or ischæmia, and he registered a preference for ischæmia, but he also wondered whether bile salts might not be the primary toxic factor. Pfältzer (1915) considered that the whole process was due to an underlying infection, as did de Lange (1924) and Biemond and van Creveld (1937). The more recent researches of the latter (de Bruyne and

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van Creveld, 1948) have thrown doubt on the importance which they originally attached to the infective process. Palm (1919) considered that liver immaturity may have played a part in the production of the jaundice, but he went no further. Hoffman and Hausmann (1926) considered that the cerebral damage was due to the release of toxic substances from damaged liver cells. Zimmerman and Yannet (1935) suggested that the nerve lesion might be due to a post-infective encephalitic process, to cerebral birth trauma or to asphyxia, or to cerebral cellular maldevelopment.

More recently six main suggestions have been put forward. First, Wiener (1946) suggested that agglutination thrombi blocked terminal capillaries in the brain causing cerebral damage; but this suggestion has received no pathological confirmation and has been retracted (Wiener and Gordon, 1948) because saline antibodies do not cross the placenta.

Secondly, that cerebral damage is a result of an antigen antibody reaction between the Rh antibody and Rh positive nerve cells, resulting in destruction of the latter. Such a conception is favoured, for example, by Bertrand (1946) and Dereymaeker (1949).

Thirdly, Darrow and Chapin (1947) have suggested, in order to explain the relative infrequency of kernicterus, that it is an anaphylactic reaction which only occurs in a sensitized subject.

Fourthly, Baar (1945) and Parsons (1947) consider that kernicterus is an hepatic encephalopathy. They suggest that damage to the liver, which is a constant finding in icterus gravis, interferes with the normal detoxicating action of the liver; toxic substances therefore accumulate and damage the nerve cells. This thesis receives support from their observation that miliary necrosis of the liver may be associated with changes in the brain not unlike those seen in cases of kernicterus. Pentschew (1948) also suggests that liver damage is primary, and that this damage leads to an inability of the brain to utilize oxygen.

Fifthly, Claireaux (1950), having reviewed the above hypotheses and having found them all wanting, has concluded that the only adequate cause for the cerebral damage is the associated anæmia and anoxia.

Finally, Küster and Krings (1950) have suggested that bilirubin itself, in excess, may cause cerebral damage; they were able to produce kernicterus in the experimental animal by the intravenous injection of bilirubin; however, the high levels needed, 100–150 mg. per 100 ml., are much greater than those encountered in cases of icterus gravis, with or without kernicterus.

The general consensus of opinion, both before the discovery of the Rh factor, and since, has agreed with Beneke (1907) that pigmentation of the brain is secondary and that the nerve cells are first damaged by a factor or factors unknown.

It is now widely realized that kernicterus is not always associated with iso-immunization, and that when it occurs in the absence of iso-

immunization the baby is usually premature (Vaughan, 1946; Zuelzer, 1949; Aidin *et al.*, 1950; Zuelzer and Mudgett, 1950; and Gerrard, 1951). In our experience the neuropathology of both types of kernicterus, i.e. whether associated with iso-immunization or not, is identical; more than 50 cases of the former group and 28 of the latter have been studied at this hospital (Baar, 1952). An identical neuropathology does not, however, necessarily imply an identical ætiology, for different factors, i.e. oxygen lack, carbon monoxide excess or hypoglycæmia, may all damage similar areas of the brain. Nevertheless a detailed study of the types both associated and unassociated with hæmolytic disease reveals many common factors and a common precipitating factor cannot be excluded.

(1) Kernicterus With or Without Hæmolytic Disease

The following analysis is based on data derived from 82 cases of kernicterus associated with hæmolytic disease (38 died in the neonatal period) and on 44 unassociated with hæmolytic disease (28 died in the neonatal period). In all cases dying the diagnosis was confirmed at necropsy; all cases surviving had a typical neonatal history which was associated with prolonged and obvious jaundice lasting from three to twelve weeks. The subsequent development of these children, in both groups, was clinically indistinguishable; all now exhibit involuntary movements, varying from chorea to dystonia, all save one are excitable and nearly all have a perceptive deafness affecting mainly the high frequencies.

(1) It is generally agreed that kernicterus associated with hæmolytic disease occurs only in the more jaundiced babies (Parsons, 1947); jaundice is also a marked feature of kernicterus without hæmolytic disease, it often seems to deepen at the onset of kernicterus, it occurs in the absence of any gross anæmia and it may persist for several months; it may even be associated with a temporary biliary obstruction.

(2) In both types of kernicterus, before or with the onset of the cerebral symptoms, a condition analogous to sclerema may be observed; the muscles feel firm and hard, resembling rigor mortis more closely than any other condition I have encountered. In severe cases the baby may set as though made of marble; such cases die; in mild cases only individual muscle groups, e.g. of thigh or calf, may be affected. This hardness of the muscles may occur more frequently in babies without hæmolytic disease, but I have observed it with both types of kernicterus; its development is, however, overshadowed if not eclipsed, by the onset of the more dramatic cerebral symptoms, and it may either remain unnoticed or it may be confused with the spasticity which may be associated with the onset of kernicterus.

(3) Both types of kernicterus are sometimes associated, terminally, with a hæmorrhagic diathesis, much bleeding occurs into the lungs and frothy blood-stained material wells up into the mouth.

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(4) Although both types of kernicterus have characteristically a latent period of one to six days before the cerebral symptoms develop they differ in two respects.

(i) The onset of kernicterus tends to be earlier in cases with hæmolytic disease, i.e. on the second to fourth day, and death, when it occurs, occurs most commonly on the fourth day of life: the onset tends to occur later in cases without hæmolytic disease, i.e. on the fourth to sixth day, and death, when it occurs, occurs most commonly on the sixth day of life, hence the term "sixth day disease" (Aidin and Tovey, 1950). Occasionally in these cases the condition of the baby is critical from birth—this was so in 4 of our cases—but this is only so in the very premature babies and is, I presume, related to the prematurity of the child rather than to the kernicterus (fig. 3).

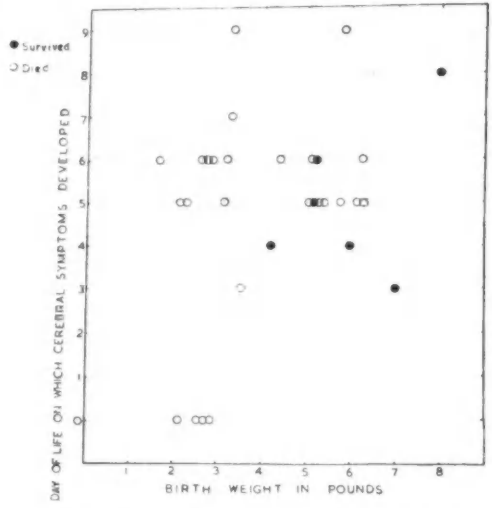

FIG. 3.—Kernicterus not associated with Rh iso-immunization, correlating the day of clinical onset of kernicterus with the fate (survival or death) of the baby.

(ii) Death, in kernicterus associated with hæmolytic disease is more certain the more rapid the onset of cerebral symptoms, it is rare in cases developing their cerebral symptoms late (fig. 1); death is not, to any appreciable extent, related to the birth-weight of the baby, the average birth-weight of 38 cases dying during the neonatal period was 6·57 lb. and of 44 cases surviving the neonatal period 6·66 lb. By contrast death in kernicterus without hæmolytic disease appears to be unrelated to the speed with which cerebral symptoms develop (fig. 4) but it is closely related to the weight of the baby at birth (fig. 5). In this respect these cases, which are predominantly premature, resemble premature babies

as a whole. The average birth-weight of 28 cases dying in the neonatal period is 3·7 lb., which is much less than the averare birth-weight, 6·1 lb., of the 16 cases which survived the neonatal period; the majority of the babies who weighed less than 5 lb. at birth died, most who weighed more than 5 lb. survived. The high mortality among the smaller babies does, however, mean that as far as the pathologist is concerned, kernicterus without hæmolytic disease is almost always confined to prematures, but the pædiatrician will encounter this same syndrome in so-called normal full-term babies and these will usually survive. In this context it should be emphasized that prematurity, in babies with hæmolytic disease, is associated with an increased incidence of kernicterus (Allen *et al.*, 1950); our own findings confirm this, the average birth-weight of 243 cases of icterus gravis being 7·3 lb., and the average birth-weight of 82 cases of kernicterus being only 6·6 lb., significantly less (fig. 4).

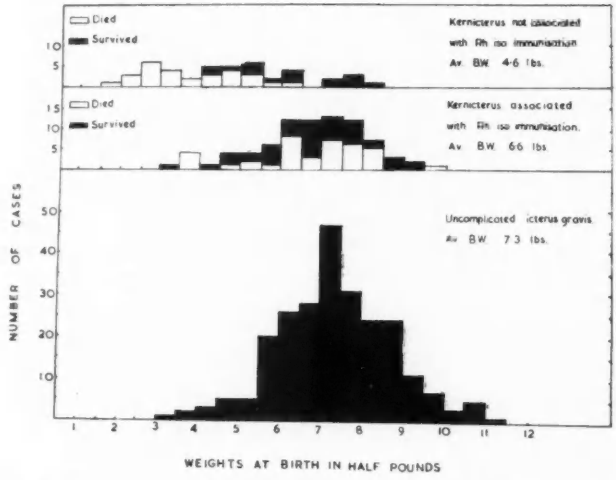

FIG. 4.—The weights at birth of babies with kernicterus (with and without hæmolytic disease) compared with the birth-weights of uncomplicated icterus gravis.

Both types of kernicterus are so similar that, without the aid of serological tests it may be difficult to decide into which group a given case falls. A perusal of Pentschew's (1948) article would never lead one to suspect, unless one had been forewarned, that prematurity and hæmolytic disease were the two most important contributory factors. A third factor to which Morganti and Beolchini (1950) and Crigler and Najjar (1952) have drawn attention is the occasional familial incidence of kernicterus, even when unassociated with haemolytic disease; we have encountered only one family in which, in the absence of iso-immunization,

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more than one child developed kernicterus, the remaining cases are sporadic.

If all cases of kernicterus have, fundamentally, a common origin only two of the theories which have been put forward are still relevant and the neural damage is either dependent on anoxia associated either with anæmia or with inadequate aeration of the lungs, or the syndrome is an hepatic encephalopathy dependent on primary destruction of liver cells either by the Rh antibody or by a toxic or infective process. That the anæmia by itself should cause the neural damage would appear to be unlikely for we have encountered no recorded instances where anæmia alone has caused similar and extensive damage to brain cells; moreover the babies who develop kernicterus are sometimes not anæmic. Deficient pulmonary ventilation, though common in prematures, has not been constant in our cases, either clinically or at necropsy; if inadequate oxygenation of the blood were a potent factor in precipitating the neural damage one might expect the development of a syndrome analogous to the "sixth day disease" in babies with severe cyanotic heart disease. An examination of the post-mortem records of the Children's Hospital, Birmingham, over the past six years reveals that necropsies have been undertaken on 32 infants under the age of 1 year with severe cyanotic heart disease, 3 died on the second day of life, 4 on the third and 2 on the fifth, 4 died in the second week and the remainder during the next eleven months. Of those dying during the first week 2 were premature and 1 had an associated intracranial birth injury; in none did the history resemble that associated with kernicterus.

Rather than subscribe unquestioningly to the theory that kernicterus is an hepatic encephalopathy it was decided to examine other possibilities.

(2) Hypoglycæmia and Cerebral Damage

It is well known that cerebral tissue needs glucose (Himwich and Nahum, 1932) and that hypoglycæmia not only causes diminished oxygen uptake by nerve-cells (Himwich *et al.*, 1939) but may also lead to irreversible cell changes (Moersch and Kernohan, 1938; Weil *et al.*, 1938; Baker, 1939; Baker and Lufkin, 1937). Moreover hypoglycæmia in the adult may lead to a loss of nerve-cells in the caudate nucleus, putamen, hippocampus, and cerebellum (Lawrence *et al.*, 1942), i.e. in the same regions as are damaged in kernicterus. The cerebral cortex may be subjected to rather less damage in the infant than in the adult, for the cortex of the infant is relatively immature (Conel, 1939; and Greenfield, 1947).

Necropsy findings in hæmolytic disease of the newborn suggest that hypoglycæmia might be expected, for not only in hydrops fœtalis (Liebegott, 1938; Gilmour, 1944) but also in kernicterus (Beneke, 1939) the islets of Langerhans are both large and numerous. Potter *et al.* (1941) go so far as to state that in nearly all cases of hæmolytic disease of the

newborn coming to necropsy there are hypertrophy and hyperplasia of the islets.

It was therefore decided to follow the blood-sugar levels in cases of hæmolytic disease, in order to find out if hypoglycæmia played any part in the production of kernicterus.

Blood-sugar levels in hæmolytic disease of the newborn.—As anticipated, 2 babies who developed kernicterus also had an associated hypoglycæmia (Gerrard, 1950). We therefore decided to estimate, as far as possible, the blood-sugar level four-hourly during the first twenty-four hours of life, the fall being greatest at this time, and thereafter twice daily (before feeds) for at least three further days. In addition we decided that our babies with hæmolytic disease should be given extra glucose, both intravenously and orally, to maintain the blood-sugar level as near to normal as possible, and blood, usually by replacement transfusion, to correct any anæmia. This line of investigation, we felt, should reveal an initial hypoglycæmia in a proportion of cases and would, if kernicterus was dependent on hypoglycæmia, prevent the development of kernicterus.

We have now followed the blood-sugar levels in 40 cases of hæmolytic disease of the newborn; the cases are not consecutive for latterly the blood-sugar levels in only the more severely affected have been followed.

The blood-sugar levels, in the initial case of kernicterus which prompted us to pursue this investigation, are illustrated in fig. 5. It is seen that the

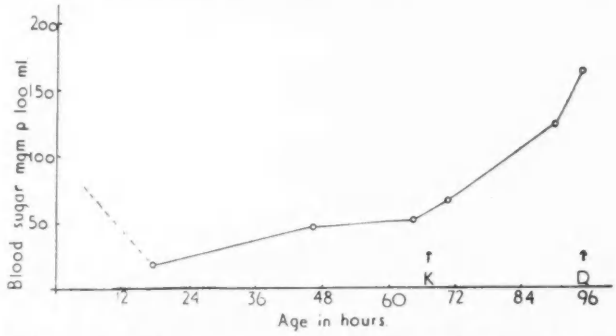

FIG. 5.—Blood-sugar levels in a baby with hæmolytic disease who developed kernicterus. Birth-weight 6 lb. 7 oz. Cord hæmoglobin 19·6 grammes per 100 ml. No replacement transfusion given.

blood sugar fell to 20 mg. per 100 ml. on the first day of life and though the blood sugar did not rise above 50 mg. per 100 ml. until the third day of life, the baby was not hypoglycæmic when kernicterus made its clinical onset; this baby was never anæmic but became deeply jaundiced. By contrast the blood-sugar levels in an uncomplicated icterus gravis are illustrated in fig. 6, in this case there was no fall in the blood-sugar level.

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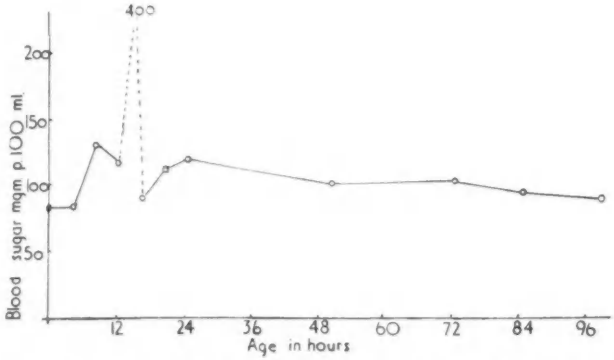

FIG. 6.—Blood-sugar levels in a baby with hæmolytic disease but without kernicterus. Birth-weight 7 lb. 10 oz. Cord hæmoglobin 11·9 grammes per 100 ml. Replacement transfusion given.

To summarize our findings, in only 12 of the 40 cases did the blood sugar fall to less than 50 mg. per 100 ml., 6 of these developed kernicterus; 28 exhibited no appreciable fall in the blood sugar and 1 developed kernicterus (fig. 8). That the fall may be rapid and that it may be

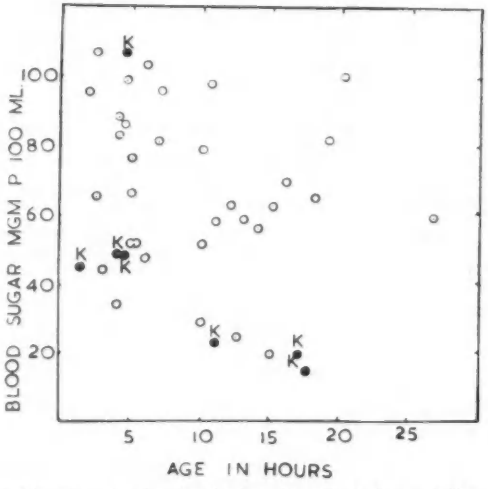

FIG. 7.—Lowest blood-sugar levels during the first day of life in 40 cases of hæmolytic disease. K = developed kernicterus.

difficult to prevent a severe degree of hypoglycæmia is best illustrated by the following case (*see* fig. 7). This infant had the lowest cord hæmoglobin in our series, i.e. 4·7 grammes per 100 ml. The initial fall in the

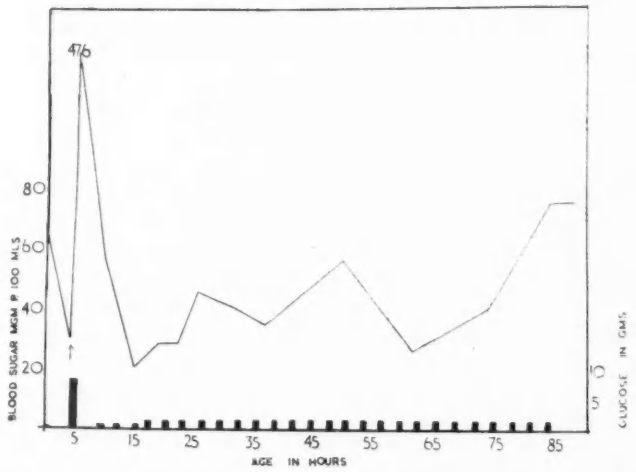

FIG. 8.—Blood-sugar levels in a severe case of hæmolytic disease, but without kernicterus. Birth-weight 6 lb. Cord hæmoglobin 4·7 grammes per 100 ml. Cord bilirubin 4·2 mg. per 100 ml.

blood sugar was checked temporarily by the replacement transfusion and by additional intravenous glucose (8 grammes) but it continued and it might well have fallen below 20 mg. per 100 ml. had not frequent oral feeds of glucose been offered; it was not until the infant was 4 days old that normal levels were maintained; the baby did not develop kernicterus. The greatest fall in the blood sugar, in our small series, occurred in a full-term baby with hæmolytic disease; in this case the blood sugar fell to 15 mg. per 100 ml. seventeen and a half hours after delivery; in spite of a replacement transfusion and 5 grammes glucose intravenously followed by frequent feeds of 20 per cent glucose, the blood-sugar level remained low (max. 31 mg. per 100 ml.), and the baby died of kernicterus on the third day of life.

The blood-sugar level in premature babies.—We have also followed the blood-sugar levels in 50 premature babies. A perusal of the relevant literature would suggest that hypoglycæmia is well tolerated by the premature baby, but Norval (1950) records 4 cases in which the blood sugar fell below 20 mg. per 100 ml.; all these babies died; the greatest fall was observed in a premature baby with erythroblastosis. In only 1 instance did a comparable fall occur in our series, in this the fall was greatest on the third day of life, when no sugar could be detected in the blood, this baby's condition was critical from an early age, but he survived in an incubator for five weeks and died of a terminal meningitis. Because of the latter complication the brain was not submitted to histological examination. The fiftieth premature developed kernicterus and died on the sixth day of life, this case exhibited no hypoglycæmia.

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Discussion

A considerable fall in the blood-sugar level was noted in a number of cases of hæmolytic disease of the newborn and in 6 of the 40 cases studied the blood sugar fell below 30 mg. per 100 ml., even though, in 5 of these, additional glucose was given both intravenously and orally. It can therefore be suggested that hypoglycæmia may play a part in the production of kernicterus and that, in conjunction with anoxia and the toxic action of bilirubin, it may lead to the destruction of those nuclear masses which, especially in the newborn period, are developing most rapidly and have great metabolic requirements. Such an interpretation, on the data we have at our disposal, is, however, hard to sustain, for the baby who was most anæmic at birth also experienced a marked hypoglycæmia and yet did not develop kernicterus. By contrast another baby, who was never very anæmic (the cord hæmoglobin was 12·5 grammes per 100 ml.), experienced no hypoglycæmia and yet developed kernicterus.

Although it would appear that hypoglycæmia is not the cause of the neural damage, or that it is no more than a contributory factor, yet it is still possible that this neural damage may have a metabolic origin, for only in this way can its distribution be most satisfactorily explained. The hypoglycæmia, it seemed, would be dependent on islet hyperplasia and hypertrophy which is such a common concomitant of hæmolytic disease of the newborn, but this did not in itself explain why the excessive growth of the islets occurred. It is reasonable to suppose that the latter arises in response to a factor in the circulation which is antagonizing the action of insulin (we have been able to demonstrate in a case of kernicterus that the islets contain an appreciable proportion of β cells); if such a factor is acting it is almost certainly present ante-partum, for even in hydrops fœtalis the islets may be both large and numerous. That there is such a substance in the circulation was suggested by one of our cases of hæmolytic disease which died at the age of 22 hours of atelectasis, and which exhibited no hypoglycæmia although the islets in this case were excessive both in size and number.

It has been suggested and it can be shown *in vitro* (Colowick *et al.*, 1947) that insulin activates hexokinase; if kernicterus is dependent on an inability to break down and metabolize glucose then the plasma of such cases might be expected to contain an inhibitor of hexokinase. Weil-Malherbe (1951) (personal communication) has been able to demonstrate such an inhibitor in the plasma of a severely affected baby with hæmolytic disease; this baby did not develop kernicterus but it required two replacement transfusions. Using Weil-Malherbe's technique I have been able to demonstrate an appreciable degree of inhibition of hexokinase activity in a case of kernicterus associated with hæmolytic disease and in a second case unassociated with hæmolytic disease. This study is in its infancy and I do not yet know whether hexokinase inhibition is or is not related to kernicterus. But some such metabolic disorder may well be found to

precipitate kernicterus and this same disorder may lead, by interfering with glucose utilization, not only to the neural damage but also to disturbed liver function (hence the jaundice) and even to disturbed muscle metabolism (hence the sclerema).

This study of both types of kernicterus, with and without hæmolytic disease, suggests that kernicterus may have a common precipitating factor which is acting maximally in babies with hæmolytic disease, hence the rapid onset and high mortality even among full-term babies; in babies without hæmolytic disease it is less active, hence its later onset, and most survive, unless they are premature, when the additional hazard nearly always leads to death. If kernicterus is fundamentally an hepatic encephalopathy then the earlier onset and greater severity among babies with hæmolytic disease is, no doubt, due to the more rapid onset and greater extent of the liver damage in these cases; in the cases without hæmolytic disease the liver damage develops more slowly and is not so severe, hence the later onset of kernicterus and the tendency for most babies, if not premature, to survive. It is, however, strange that the neonatal brain, which is so much less sensitive to oxygen lack and to hypoglycæmia than is the adult organ, should nevertheless react so dramatically to liver damage and to jaundice; the latter rarely, if ever, produces analogous neural damage in the more sensitive adult organ. It is for this reason amongst others that the liver damage may not be primary but be secondary to a biochemical disorder, e.g. hexokinase inhibition; the latter, although physiological *in utero*, may lead to irreparable brain damage if it persists for long after delivery. At birth the newborn child has to adapt itself to a new mode of life, and certain biochemical readjustments are required of it, for it is suddenly deprived of a relatively limitless maternal supply of nourishment; it must suddenly reverse its *modus vivendi*, and instead of building up stores from the maternal supply it must begin to break down its own stores. It may be that a delay in this readjustment, possibly aggravated by liver damage, deprives the liver, brain and even muscles of essential nutriment and so leads to deepening jaundice and to kernicterus, and even, in some instances, to sclerema.

Acknowledgments

It gives me great pleasure to acknowledge my indebtedness to Dr. J. G. Greenfield for his interest and help in this study. I am also especially indebted to Dr. H. S. Baar, who has put his pathological material at my disposal and has helped me in its interpretation, to Dr. Barbara Davies, to Dr. Betty E. Howarth and to Miss S. A. Barnett who assisted in the study of the blood-sugar levels in prematures and in babies with hæmolytic disease, and to Dr. J. M. Jefferson for his advice and help. I am also grateful to Dr. F. Braid, Dr. V. Mary Crosse, to Professor J. M. Smellie and to the staff of the Children's Hospital, Birmingham, for permission to study their cases, to Dr. A. E. Mourant and to Dr. W.

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Weiner for undertaking the serological investigations and to Mr. J. G. Williamson for the illustrations.

REFERENCES

AGASSIZ, C. D. S., O'DONNELL, M. B., and COLLIS, E. (1949) *Lancet* (ii), 1030.
AIDIN, R., CORNER, B., and TOVEY, G. (1950) *Lancet* (i), 1153.
——, and TOVEY, G. H. (1950) *J. Clin. Path.*, **3**, 376.
ALEXANDER, L. (1942) *Res. Publ. Ass. nerv. ment. Dis.*, **21**, 77.
ALLAN, F. G. (1950) Personal communication.
ALLEN, F. H., DIAMOND, L. K., and VAUGHAN, V. C. (1950) *Pediatrics*, **6**, 441.
ALLEN, W. F. (1940) *Amer. J. Physiol.*, **128**, 754.
—— (1941) *Amer. J. Physiol.*, **132**, 81.
ARKWRIGHT, J. A. (1902) *Edinb. med. J.*, **2**, 156.
BAAR, H. S. (1945) *Austr. med. Bull.*, 1. Special issue.
—— (1952) Personal communication.
BAKER, A. E. (1939) *Amer. J. Psychiat.*, **96**, 123.
——, and LUFKIN, N. H. (1937) *Arch. Path.*, **23**, 190.
BECKER, P. F. L., and VOGEL, P. (1948) *J. Neuropath. Exp. Neurol.*, **7**, 190.
BENEKE, E. (1939) *Zbl. allg. Path. Anat.*, **72**, 401.
BENEKE, R. (1907) *Munch. med. Wschr.*, **54**, 2023.
BERTRAND, I. (1946) *Rev. Hémat.*, **1**, 399.
BIEMOND, A., and VAN CREVELD, S. (1937) *Arch. dis. Childh.*, **12**, 173.
VAN BOGAERT, L. (1947) *Ann. Pædiat.*, **168**, 57.
BRODAL, A. (1947) *Brain*, **70**, 179.
DE BRUYNE, J. I., and VAN CREVELD, S. (1948) *Arch. Dis. Childh.*, **23**, 84.
BUCY, P. C. (1942) *Res. Publ. Ass. nerv. ment. Dis.*, **21**, 551.
——, and BUCHANAN, D. N. (1932) *Brain*, **55**, 479.
BURGHAARD, E., and SCHLEUSSING, H. (1933) *Klin. Wschr.*, **2**, 1526.
CAPPELL, D. F. (1947) *Brain*, **70**, 486.
CARLSON, E. R. (1941) Born that way. New York.
CHOWN, B. (1948) *Blood*. Special issue. **2**, 155.
CLAIREAUX, A. (1950) *Arch. Dis. Childh.*, **25**, 61.
CLARK, W. E. LE GROS, and MEYER, M. (1947) *Brain*, **70**, 304.
COLOWICK, S. P., CORI, G. T., and STEIN, M. W. (1947) *J. Biol. Chem.*, **168**, 583.
CONEL, J. L. (1939) Postnatal Development of the Human Cerebral Cortex, Harvard University Press.
COQUET, M. (1944) *Ann. Pædiat.*, **163**, 83.
CRABTREE, N. L., and GERRARD, J. W. (1950) *J. Laryngol.*, **64**, 482.
CREAK, M. (1947) *Arch. Dis. Childh.*, **22**, 181.
CRIGLER, J. F. and NAJJAR, V. A. (1952) Pediatrics, **10**, 169.
CROSSE, V. M. (1950) Personal communication.
DARROW, R. R., and CHAPIN, J. (1947) *Amer. J. Dis. Child.*, **73**, 257.
DAVISON, C. (1942) *Res. Publ. Ass. nerv. ment. Dis.*, **21**, 267.
DENNY-BROWN, D. (1950) *J. nerv. men. Dis.*, **112**, 1.
DEREYMAEKER, A. (1949) L'Ictère nucleaire du nouveau-ne. Paris.
DIAMOND, L. K. (1945) *New Engl. J. med.*, **232**, 447 and 475.
DOW, R. S. (1938*a*) *Arch. Neurol. Psychiat. Chicago*. **40**, 500.
—— (1938*b*) *J. Comp. Neurol.*, **68**, 297.
DUBLIN, W. B. (1951) *Amer. J. Clin. Path.*, **22**, 935.
ESCH, P. (1908) *Ztrbl. Gynäk.*, **32**, 969.
EVANS, P. R. (1948) *Arch. Dis. Childh.*, **23**, 213.
——, and POLANI, P. E. (1950) *Quart. J. med. N.S.*, **19**, 129.
FITZGERALD, G. M., GREENFIELD, J. G., and KOUNINE, B. (1939) *Brain*, **62**, 292.

FORD, F. R. (1945) Diseases of the Nervous System in Infancy, Childhood and Adolescence. Springfield, Illinois.
GERRARD, J. (1950) *Lancet* (ii), 35.
—— (1951) Dissertation for D.M. Oxon.
—— (1952) *J. Laryngol.*, **66**, 39.
GERVER, J. M., and DAY, R. (1950) *J. Pediat.*, **36**, 342.
GILMOUR, D. (1950) *J. Ment. Sci.*, **96**, 359.
GILMOUR, J. R. (1944) *Arch. Dis. Childh.*, **19**, 1.
GIUNTINI, R. (1942) *Riv. Clin. Pediat.*, **40**, 513.
GOWERS, W. R. (1906) *Rev. Neurol. Psychiat.*, **39**, 971.
GREENFIELD, J. G. (1947) *Lancet* (ii), 444.
GUTHRIE, L. (1913) *Proc. R. Soc. Med.*, **7**, 86.
HART, A. P. (1925) *Canad. med. Ass. J.*, **15**, 1008.
HERZ, E. (1944) *Arch. Neurol. Psychiat. Chicago*, **4**, 249.
HIMWICH, H. E., FROSTIG, J. P., FAZEKAS, J. F., and HADIDIAN, Z. (1939) *Amer. J. Psychiat.*, **96**, 371.
—— and NAHUM, L. A. (1932) *Amer. J. Physiol.*, **101**, 446.
HOFFMANN, W., and HAUSMANN, M. (1926) *Monats. f. Kinderheilk.*, **33**, 193.
HORSLEY, V. (1890) *Brit. med. J.* (ii), 1286.
—— (1908) *Brit. med. J.* (ii), 129.
HUNT, J. R. (1917) *Brain*, **40**, 58.
JACKSON, J. HUGHLINGS, and BEEVOR, C. E. (1890) *Brain*, **12**, 346.
KENNARD, M. A. (1944) *J. Neuropath. Exper. Neurol.*, **3**, 289.
KÜSTER, F., and KRINGS, H. (1950) *Lancet* (i), 974.
LANDE, L. (1948) *J. Pediat.*, **32**, 693.
DE LANGE, C. (1924) *Acta paediatr. Stockh.*, **4**, 60.
LASSEK, A. M. (1948) *Res. Publ. Ass. nerv. ment. Dis.*, **27**, 106.
LAWRENCE, R. D., MEYER, A., and NEVIN, S. (1942) *Quart. J. Med.*, **35**, 181.
LIEBEGOTT, C. (1938) *Beitr. path. Anat.*, **101**, 319.
MAGNUS, R. (1926) *Lancet* (ii), 531.
——, and DE KLEJN (1912) *Pflug Arch. ges. Physiol.*, **145**, 455.
MOERSCH, F. P., and KERNOHAN, J. W. (1938) *Arch. Neurol. Psychiat. Chicago*, **39**, 242.
MORGANTI, G. and BEOLCHINI, P. E. (1950) Atti del 1° Congresso Giuliano di Nipiologia, p. 39.
MURPHY, J. P., and GELLHORN, E. (1945) *J. Neurophysiol.*, **8**, 337.
NORVAL, M. A. (1950) *J. Pediat.*, **36**, 177.
ORTH, J. (1875) *Virchows Arch.*, **63**, 447.
PALM, H. (1919) *Machr. Geburtsh. Gynak.*, **49**, 264.
PAPEZ, J. W. (1937) *Arch. Neurol. Psychiat. Chicago*, **38**, 725.
——, HERTZMAN, J., and RUNDLES, R. W. (1938) *Arch. Neurol. Psychiat. Chicago*, **40**, 789.
PARSONS, L. G. (1947) *Lancet* (i), 815.
—— (1949) *Brit. med. J.*, **1**, 234.
PENTSCHEW, A. (1948) *Archiv. f. Psych. u. Neurol.*, **180**, 118.
PERLSTEIN, M. (1950) *Amer. J. Dis. Child.*, **79**, 605.
PFÄLTZER, B. (1915) *Z. Geburtsh. Gynäk.*, **76**, 685.
PHELPS, W. M. (1941) *New York St. J. Med.*, **41**, 1827.
PICKLES, M. M. (1949) Hæmolytic Disease of the New born. Oxford.
POTTER, E. L., SECKEL, H. P. G., and STRYKER, W. A. (1941) *Arch. Path.*, **31**, 467.
RACE, R. R. (1946) *Brit. med. Bull.*, **4**, 188.
RANSON, S. W., FISHER, C., and INGRAM, W. R. (1937) *Arch. Neurol. Psychiat. Chicago*, **38**, 445.
SCHMORL, G. (1903) *Verh. dtsch. path. Ges.*, **6**, 109.

XUM

SCHUSTER, P. (1937) *Arch. Psychiat. Nervenk.*, **106**, 201.
SHERRINGTON, C. S. (1898) *J. Physiol.*, **22**, 319.
SNYDER, L. H., SCHONFELD, M. D., and OFFERMAN, E. M. (1945) *J. Hered.*, **36**, 9.
SOBEL, I. P., and ZUCKER, J. M. (1940) *J. Pediat.*, **4**, 445.
SPILLER, W. G. (1915) *Amer. J. med. Sci.*, **149**, 345.
VAUGHAN, V. C. (1946) *J. Pediat.*, **29**, 462.
WALSHE, F. M. R. (1947) *Brain*. **70**, 329.
WECHSLER, I. S. (1938) *Arch. Neurol. Psychiat. Chicago*, **39**, 971.
WEIL, A., LIEBERT, E., and HEILBRUNN, G. (1938) *Arch. Neurol. Psychiat. Chicago*, **39**, 467.
WEIL-MALHERBE, H. (1951) Personal communication.
VAN WESTRIENEN, A. (1935) *Maandschr. v. Kindergeneesk.*, **4**, 454.
—— (1936) *Maandschr. v. Kindergeneesk.*, **5**, 434.
——, and DE LANGE, C. (1937) *Jb. f. Kinderheilk.*, **150**, 257.
WHYTT, R. (1768) Observations on the Dropsy of the Brain.
WIENER, A. S. (1946) *Amer. J. Dis. Child.*, **71**, 14.
——, and GORDON, E. B. (1948) *J. Lab. clin. Med.*, **33**, 181.
WILSON, S. A. K. (1928) Modern Problems in Neurology.
—— (1940) Neurology. Vol. 2.
YANNET, H., and LIEBERMAN, R. (1944) *Am. J. Ment. Deficiency*, **49**, 133.
——, —— (1946) *J. Amer. med. Ass.*, **130**, 1, 335.
——, —— (1950) *Pediatrics*, **5**, 329.
YLLPÖ, A. (1918) *Z. Kinderheilk.*, **17**, 334.
ZIMMERMAN, H. M., and YANNET, H. (1933) *Amer. J. Dis. Child.*, **45**, 740.
——, —— (1935) *Amer. J. Dis. Child.*, **49**, 418.
ZUELZER, W. W. (1949) *Pediatrics*, **4**, 269.
——, and MUDGETT, R. T. (1950) *Pediatrics*, **6**, 452.

RESIDUAL NEURONS IN THE HUMAN THALAMUS FOLLOWING HEMIDECORTICATION

BY

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Introduction

It has been well established by partial lesions of the cerebral cortex that most of the principal nuclei of the thalamus severally project to one or other of the areas of the cerebral cortex. On the other hand, the total projection of the thalamus to the cerebral cortex has been investigated in experimental animals by studying the retrograde cell degeneration following complete (or almost complete) hemidecortication. Although after such a lesion the majority of the cells in the cortically dependent nuclei disappear, a certain number have been found to persist in the rat (Combs, 1949, 1951) and in the monkey and chimpanzee (Walker, 1938*a* and 1938*b*). In the human brain, also, in which the thalamus has undergone severe atrophy as the result of extensive pathological lesions of the cortex, some cells in the corresponding thalamic nuclei have been found to persist (Le Gros Clark and Russell, 1940; Sheps, 1945). The significance of these "residual neurons" of the thalamus is unknown, but the fact that they do not undergo true retrograde degeneration suggests that they do not connect to the cortex, or at least not exclusively so. It is possible, therefore, that they may serve important functions of a sensory nature at a subcortical level, and for this reason it is desirable to obtain more precise information of their number and distribution.

The following case has provided an opportunity for studying the retrograde cell degeneration in the human thalamus after a practically complete hemidecortication, with special reference to residual neurons.

Case report.—J. A. T., a man of 36, who was an advanced schizophrenic, was transferred to the Radcliffe Infirmary from a mental hospital in January 1951. At the age of 3 months his right eye had been enucleated for infantile glaucoma and following this weakness of the right arm was noted. As he developed it was seen that his right hand and foot were shrunken. He was mentally retarded and during adolescence he had compulsive urges. In 1946 he became unmanageable, and in the following year was admitted to a mental hospital. At no stage did he suffer from epileptic fits.

On examination he was found to be well orientated, and there was no aphasia. There was a marked weakness of the right lower face. The right hand was grossly deformed and held in an athetotic posture, and there were continuous spontaneous

[1]Holding a Medical Research Council Fellowship in Clinical Research.

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movements of the thumb and index finger. The right upper limb was 3 inches shorter than the left and all the muscles were profoundly wasted; only very slight motor power remained at the wrist and in the fingers. The right leg was an inch shorter than the left and there was a moderate pes cavus deformity; motor power was only slightly diminished at all joints. All the tendon reflexes were brisker on the right side, with the exception of the ankle-jerks which were equal. The right plantar reflex was extensor. Light touch was poorly appreciated on the right arm and position-sense was equivocal on the right side; pin-prick and vibration sense were normal. His vocabulary and use of words corresponded with a mental age of 14 but in non-verbal fields his ability was below that of a child of 8. The C.S.F. showed no abnormality. Ventriculography demonstrated a virtually normal ventricular system.

On February 26, 1951, a left cerebral hemispherectomy was performed by Sir Hugh Cairns, the hemisphere being dissected off the basal ganglia. Post-operatively he had many attacks of left-sided focal epilepsy and died on March 22.

The resected left cerebral hemisphere did not show any gross abnormality. Blocks were taken from the main cortical areas and the sections were stained with toluidin blue, Van Gieson and Loyez hæmatoxylin. Examination of these showed no evident change in the morphology or lamination of the cells. The underlying white matter showed no loss of myelin nor were there any areas of gliosis.

Summary of necropsy.—There was some bronchopneumonic consolidation and pus was present in the bronchi of both lungs. Most of the large intracranial venous sinuses contained ante-mortem clot. In the parietal and occipital lobes of the right cerebral hemisphere there was a massive infarction and recent hæmorrhage which presumably occurred some hours before death. Of the left cerebral hemisphere the only cortex remaining included the posterior 3·7 cm. of gyrus rectus with some of the adjacent orbital cortex, and about 1 cm.^{2} of the cingular gyrus anteriorly (fig. 1). Most of the caudate and lentiform nuclei had been spared; the thalamus and hypothalamus together with the amygaloid region and hippocampus were intact. The left cerebral peduncle and pyramidal tract were wasted; the left lateral cerebellar lobe and inferior olive were both smaller than those of the right side. The right half of the spinal cord was smaller than the left and the right optic nerve showed marked atrophy.

Material and Methods

Blocks containing the whole of the thalamus and basal ganglia of both sides were embedded in celloidin and serial sections cut throughout their entire antero-posterior extent. Every eighth section was stained with toluidin blue and systematically studied in order to determine the cellular atrophy which had occurred. Due to the fact that the remnant of the left hemisphere had retracted backwards during the post-operative period, comparable levels on the two sides were on different sections. Allowance for this was made when comparing the cells of the normal and affected sides, the comparison being made always at strictly comparable levels.

In assessing the degree of degeneration in the cells of the thalamic nuclei, the appearance of the Nissl substance, the density of staining and the shrinkage of the cell body were taken as criteria. An excentric position of the nucleus within the cell body was not by itself used as a sign of degeneration as many normal cells in the unaffected thalamus were seen also to have excentric nuclei. Thus, in 100 cells selected at random at three comparable levels on both sides the nucleus was found

to be central in only 20–30 per cent of these cells on the two sides. Approximately, this is the figure that would be expected if the nucleus were randomly situated in the cell. Similar figures were obtained for the cells in the normal thalamus of a macaque monkey. It appears, therefore, that a central position of the nucleus is not typical for the cells of the thalamus. Warwick (1950) in his study of retrograde degeneration in the oculomotor nucleus of monkeys also states that "excentricity of the nucleus was not always a marked feature," and in a study of transneuronal cell atrophy in the cat Cook, Walker and Barr (1951) note that in the lateral geniculate nucleus the nuclei of normal cells of lamina pars dorsalis A are frequently excentric.

In the ventral and lateral nuclei many well-preserved cells were found. In order to determine what proportion of the original cell population persisted a series of counts was made. In each of the ventral nuclei the cells were counted in ten fields selected at random so as to cover the whole area of the nucleus. In the posterior ventral nuclei these samples were taken at three different levels, anterior, middle and posterior, and in the nucleus ventralis lateralis and the nucleus ventralis anterior at about the middle of their anteroposterior extent. The counts were made with a projection apparatus; the fields were projected at a fixed magnification throughout and all cells in which the nucleus could be seen were traced and counted. These samples were taken at comparable levels on both sides. Further, in order to determine the variation in cell size in the normal ventral nuclei and whether there had been a selective degeneration of cells of different sizes on the affected side, the diameters of 100 cells were measured at comparable levels on the two sides. For this purpose cells in which distinct nucleoli could be seen were taken at random; the diameter of the long axis of the cells and the maximum diameter at right angles to this were measured by means of a screw-micrometer eyepiece. The areas of the cells were estimated approximately by assuming that these were the long and short axes of an ellipse. Histograms were prepared by plotting cell areas against number of cells.

Microscopical Examination

Approximately the anterior 5 mm. of the corpus striatum has been completely destroyed. At a level just in front of the optic chiasma the medial margin of the striatum appears, and behind this increasing amounts of the caudate nucleus and putamen have been spared. Approximately half of the head and most of the body of the caudate nucleus remain; a small but varying extent of necrosis, however, has involved the ventricular margin of the remaining portion. The cross-sectional area of the remaining part of the putamen varies in different sections from half to two-thirds of that on the unaffected side; there is a narrow peripheral border of necrosis and gliosis but nowhere does this extend far into the nucleus. Away from the necrotic areas and the accompanying glial reaction the normal cyto-architecture of both these elements is preserved; the cells have a normal appearance and density.

The globus pallidus is intact, but as compared with the opposite side the density of the cells is diminished. Anteriorly this is seen in the lateral part where about half of the cells have disappeared; in more posterior planes the reduction is less marked and involves also the medial part of the nucleus. Many of the remaining cells contain lipochrome pigment whereas on the unaffected side this is found only in an occasional cell: slight gliosis is present, more marked in the lateral part and in the band of fibres between the medial and lateral portions.

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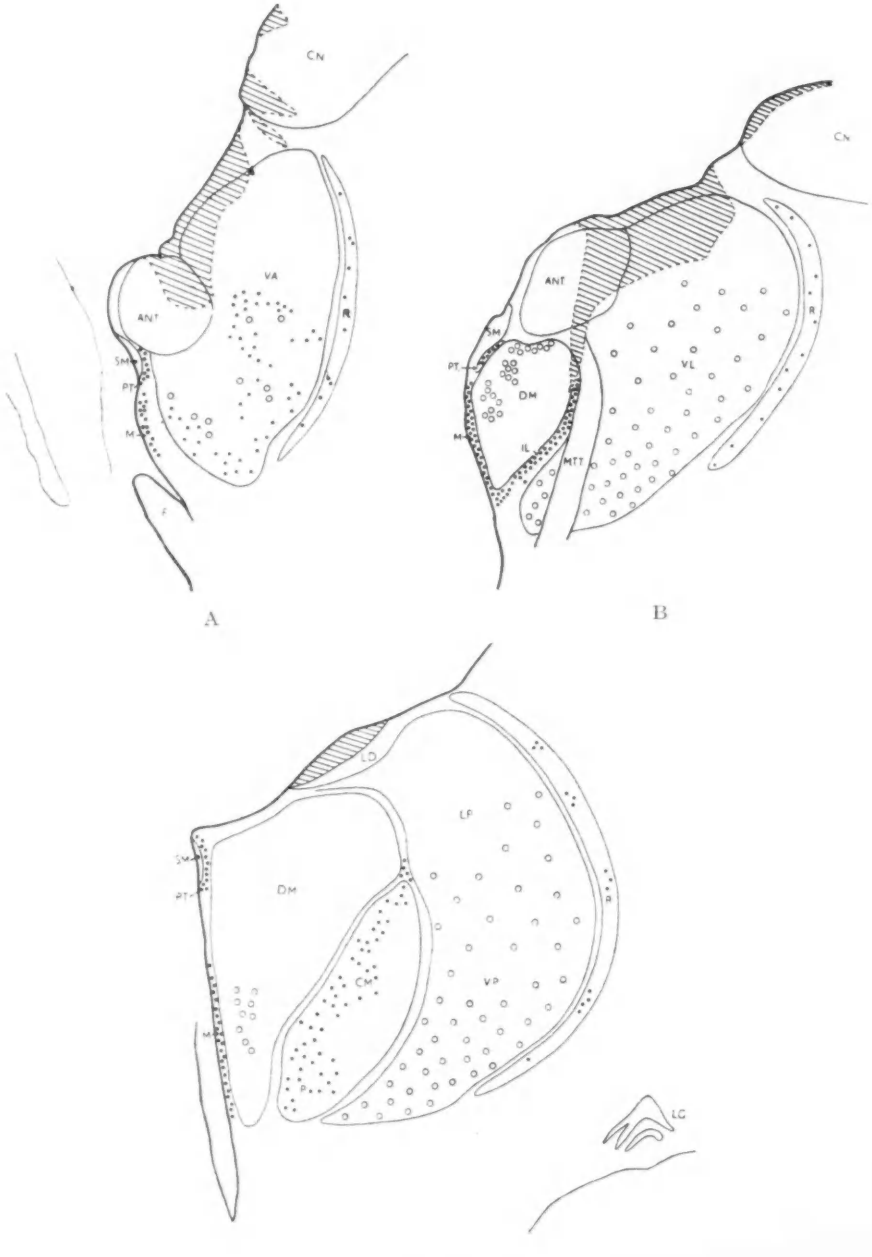
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FIG. 2.

THALAMUS

Anterior nucleus.—The lateral half of this nucleus has been destroyed by the operative resection and the consequent gliosis (fig. 2A). No normal cells are present in the remaining portion. Those that do remain are grossly degenerated; they are severely shrunken, stain very feebly and contain no demonstrable Nissl substance.

Medial nuclei.—The dorsomedial nucleus has shrunk in volume and has undergone severe degeneration; however, its outline can be readily defined by the normal cells of the adjacent mid-line and intralaminar nuclei (fig. 3). Many of the cells have disappeared and the majority of those that remain are very pale and shrunken, with no distinct Nissl granules. There are, however, small collections of well-preserved cells which extend in scattered groups throughout the central part of the nucleus. Anteriorly they are situated towards the dorsomedial corner of the nucleus but posteriorly they occupy a more ventral position (fig. 2 B and C). These cells stain less deeply than those on the unaffected side; the Nissl substance is reduced and is found at the periphery of the cell, but otherwise they appear normal. A narrow band of cells with similar staining properties lies along the dorsal border and extends a short distance down the medial edge. This band is more prominent in the anterior half of the nucleus; it corresponds in position to the region which McLardy (1950) regards as equivalent to the magnocellular element in lower primates. There is a moderate degree of gliosis which is more marked posteriorly.

The nucleus submedius could not be distinguished with certainty. McLardy (1950) has reported it as being an inconstant element in the human thalamus.

Ventral and lateral nuclei.—The operative resection has involved the dorsal borders of these nuclei and the subsequent necrosis and gliosis have destroyed the normal cyto-architecture in the immediately adjacent regions. In the anterior half of nucleus lateralis posterior severe degeneration has occurred and only an occasional cell is seen. In the other elements of this group, however, many well-preserved cells

FIG. 2.—Diagrams of coronal sections of the affected thalamus drawn with a projection apparatus. A, near the anterior end of the thalamus; B, a short distance behind the anterior end of the dorsomedial nucleus; and C, about the middle of the thalamus. Areas damaged by the surgical resection are indicated by hatching, the distribution of normal residual cells by dots and the distribution of residual cells showing reduction of Nissl substance by circles. ANT., Anterior nuclei. V.A., nucleus ventralis anterior. R., reticular nucleus. M., mid-line nuclei. P.T., paratænial nucleus. V.L., nucleus ventralis lateralis. D.M., dorsomedial nucleus. IL., intralaminar nuclei. L.P., nucleus lateralis posterior. L.D., nucleus lateralis dorsalis. V.P., nucleus ventralis posterior. C.M., centre-median nucleus. L.G., lateral geniculate nucleus. S.M., stria medullaris. M.T.T., mammillo-thalamic tract. C.N., caudate nucleus.

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persist; the sample counts show that these cells amount to 40–50 per cent of the normal total (Table I). Though the counts suggest that there

TABLE I

Nucleus	*Mean counts of cells in ten fields*		*Percentage residual cells*
	Normal side	*Affected side*	
Nucleus ventralis Anterior	19·8	11·3	57
Nucleus ventralis Lateralis	18·1	9·9	55
Nucleus ventralis Posterior Anterior level ..	25·9	12·4	48
Nucleus ventralis Posterior Middle level ..	24·2	11·9	49
Nucleus ventralis Posterior Posterior level ..	27·2	10·6	39

is a slight difference in the proportion that remain in the different subdivisions of the ventral nuclei, statistical analysis shows that this variation is not significant.

In the nucleus ventralis anterior about half of the cells that remain are quite normal in appearance and these are found chiefly in the ventral and lateral parts of the nucleus. Of the other cells that remain in the nucleus ventralis anterior, and all those that persist in the other nuclei, the majority do not stain quite so deeply as those in the normal thalamus (though direct comparison of the two sides by means of a comparison eyepiece shows that the variation in the depth of staining of these residual cells does overlap the normal range of variation on the opposite side). The Nissl substance is reduced in amount and is situated at the periphery of the cell-body and many of the cells contain lipochrome pigment. On the other hand their cell-processes are distinct and in their general appearance they otherwise appear well preserved (figs. 4 and 5). As may be seen by reference to the histograms (fig. 6) in the normal nucleus ventralis lateralis and ventralis posterior the cell-size shows a bimodal distribution, with means about 500 μ^2 and 1,700 μ^2. In the nuclei of the affected side, the variation in size is distributed evenly about a mean of 1,100 μ^2. At first sight it thus appears that the retrograde degeneration has affected predominantly the cells of the small size group, but there is also the possibility that some of these residual cells may be small cells which have undergone swelling. The preserved cells are distributed fairly uniformly but appear to be rather more numerous at the ventral margins of the nuclei. The glial reaction is dense in the nucleus ventralis anterior and nucleus lateralis posterior but relatively slighter in the other components of this group.

Pulvinar.—Severe degeneration has occurred in this element and practically all the cells have disappeared; they have been replaced by an intense glial reaction which is more severe than in any other nucleus. The few scattered cells which persist are shrunken, stain very faintly, and have no Nissl granules.

The *nucleus limitans* stands out clearly along the medial edge of the pulvinar; its constituent cells are normal in appearance, and comparison with the opposite side shows no apparent change in their density. The slight gliosis present is probably the result of degeneration of fibres of passage.

Centre-median nucleus.—In this nucleus partial degeneration has occurred, the degree and distribution of cell-loss varying at different cross-sectional levels. Throughout its whole anteroposterior extent cells remain along the medial and dorsal margins, and in the middle third they are also present in the medial half of the nucleus. Counts made at these sites show that the cells are approximately half of normal density. Most of the cells appear quite normal as compared with those of the other side. A moderate degree of gliosis is seen at anterior levels but there is a more severe reaction posteriorly.

The adjoining parafascicular nucleus is very well preserved; the cells stain normally and are of normal density. There is no clear demarcation between this element and the centre-median nucleus.

Nuclei of the mid-line.—These stand out and are sharply defined in contrast with the degeneration in the adjacent dorsomedial nucleus. The cells show no appreciable difference in morphology or density from those at comparable levels on the opposite side (fig. 6).

Intralaminar nuclei.—These also persist with no apparent change; their cells stain normally and are of normal density. There is a slight gliosis presumably due to degeneration of fibres of passage.

Nucleus reticularis.—Throughout the whole extent of this nucleus there is a marked diminution in the number of cells. The density varies, however, at different anteroposterior levels and also in the vertical extent of the nucleus in any given section. In most sections the nucleus is represented by clusters of two or three cells separated by wide intervals. Owing to this variation it is very difficult to say whether the degree of degeneration is correlated with that in the adjacent ventral and lateral nuclei. Those cells that do persist appear quite normal compared with those in the opposite nucleus, but among them there is an increased number of glial cells.

Medial geniculate nucleus.—This has undergone practically complete degeneration; very few scattered cells remain and only the faint outlines of these can be distinguished. There is also a severe degree of gliosis present.

Lateral geniculate nucleus.—In the lateral geniculate nucleus of both sides the cells in the laminæ which received fibres from the right eye (enucleated in infancy) have undergone transneuronal degeneration and have been replaced by bands of gliosis. On the left side the cells in the three laminæ, 2, 3 and 5, show retrograde degeneration as a result of the hemispherectomy. In the small-celled laminæ the cells are severely

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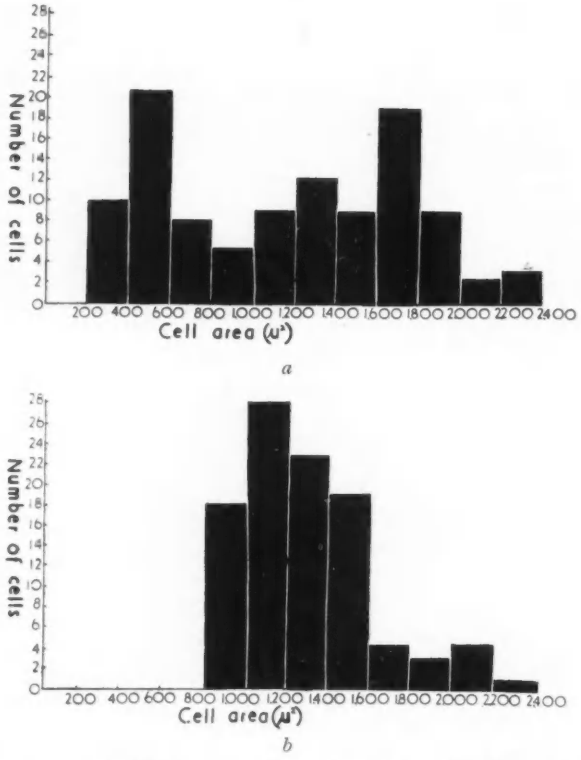

FIG. 6.—Frequency distribution of cell size in the nucleus ventralis posterior, normal side (*a*) and affected side (*b*).

shrunken, stain very faintly and contain no Nissl granules. The degeneration in the ventral large-celled laminæ appears to be less extreme and even under low magnification its constituent cells are distinguished by their deeper staining. This difference is presumably related to their much larger size, for when compared with the normal cells of the large-celled lamina on the opposite side they are actually seen to be grossly degenerated. They are shrunken and weakly stained, and the cell-processes have disappeared. In the cytoplasm of most of the cells granules of lipochrome pigment can be seen and the Nissl substance is either greatly reduced and situated at the periphery of the cell or it had completely disappeared.

DISCUSSION

One of the striking features of this case is that all the cells which still persist in the affected thalamus fall into one of three categories. Some

cells are quite normal in appearance. The second category is composed of cells which do not stain quite so deeply as on the normal side and in which the Nissl substance is reduced and is situated peripherally; however, these cells appear to be otherwise well preserved and normal. The third type of cell stains very feebly, is severely shrunken and has no Nissl granules; it is reasonable to assume that these cells would have disappeared completely if the post-operative survival had been longer.

The cells of the second category are found in the dorsomedial nucleus and in the nuclei of the ventral and lateral group. In the dorsomedial nucleus the relatively small number of these well-preserved cells (some of them comprising the magno-cellular element) may be attributed in part to connexions with the hypothalamus and in part to connexions with the posterior orbital cortex which was spared, as the site of these cells in the nucleus conforms with McLardy's diagram (1950) of the thalamic projection to areas 11 and 47.

The residual neurons in the posterior and lateral ventral nuclei have not such an obvious explanation, as all the cortex to which these nuclei project has been removed and there is as yet no definite evidence that they send fibres elsewhere. After hemidecortication in monkeys and chimpanzees the presence of similar residual cells in the ventral and lateral nuclei has been reported by Walker (1938*a*, 1938*b*), and following hemidecortication in rats Combs (1949) found that some cells persist in all the nuclei of the thalamus except the nucleus lateralis. After extensive pathological lesions of the cerebral cortex in human brains of several years' duration, residual neurons have been described in the ventral and lateral nuclei by Le Gros Clark and Russell (1940) and by Sheps (1945). In the present case it has been found that these cells amount to 40–50 per cent of the normal number of cells in the nuclei and that there is no significant difference in their number in the different subdivisions of the ventral group. The fact that the residual neurons in the posterior ventral and lateral ventral nuclei are predominantly large cells is clearly of some significance. This observation is in agreement with Sheps who noted that "The larger neurons, in the main, had the normal staining characteristics and appeared to be present in normal numbers. There was a falling out of small neurons, however, and many of them were shrunken and degenerated." In monkeys and rats residual neurons have been found two to three months after hemidecortication and (as noted above) they have also been described in human brains several years after the occurrence of cortical damage. Such observations indicate that the persistence of these cells is not due simply to a slow rate of true retrograde degeneration; and, if this were the explanation, a graded series of progressively degenerating cells might be expected rather than well defined and contrasting groups of cells which are either grossly degenerated or approximate to the normal. Relevant to this is Brodal's (1939) finding in the inferior olive where he found in mature rabbits and mice that all

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the cells which were going to disappear after cerebellar lesions did so within sixteen days and that after this the number of residual cells remained constant. It has been suggested by Walker (1938*a*) that such residual cells in the thalamus are intercalated neurons with essentially intrathalamic connexions and that they serve to connect the cells of the ventral nuclei (in connexion with which the ascending sensory fibres end) with the cells of "association" nuclei such as nucleus dorsomedialis and pulvinar. The relatively slight changes which do occur in these cells after removal of the cortex may be due to transneuronal degeneration or disuse atrophy.

Cook, Walker and Barr (1951) have made a detailed study of the transneuronal cell degeneration in the lateral geniculate nucleus of the cat and rabbit. They found the cells unchanged thirty-two days after enucleation of the eye but by sixty-three days both the nuclei and cell-bodies of these lateral geniculate neurons had decreased in size. The Nissl substance underwent a very slow progressive reduction and became displaced towards the periphery of the cell; the cytological picture was thus different from that of chromatolysis. Vacuolation of the cytoplasm occurred after eight to ten months. In their appearance the residual cells found in the present case are somewhat similar to the cells described by these authors and this strongly suggests that they may be undergoing transneuronal degeneration. It may be noted, also, that according to the observations of Glees and Le Gros Clark (1941) transneuronal degeneration in the lateral geniculate nucleus of the monkey is evident much earlier after section of the optic nerve than in the cat and rabbit. The view that these cells may be undergoing transneuronal degeneration is in accord with the observations of M. Meyer (1949) on the terminal degeneration in the human thalamus after the operation of leucotomy. This author demonstrated severe terminal degeneration in the nucleus ventralis anterior, nucleus ventralis lateralis and in the reticular nucleus after undercutting of the cortex of area 6 and possibly of areas 8 and 9. The extent and importance of the degeneration present in these ventral nuclei was found to be much greater than that in the dorsomedial nucleus due to isolation of the prefrontal cortex. It has also been suggested (Le Gros Clark, 1949) that some cells persist in the thalamus because, in addition to sending their main axon to the cortex, they also send a collateral to the association nuclei of the thalamus; the preservation of the cell is then due to the presence of this functional collateral. It should be noted that Brodal (1940), using young rabbits and his modification of Gudden's method, obtained degeneration of all the cells in the inferior olive after cerebellar lesions, but it remains possible that this difference between young and adult animals may be due to the development of functional collaterals during the growth of the animal.

The normal cells found in the nucleus ventralis anterior are possibly

due to the preservation of the globus pallidus, as Ranson and Ranson (1942) observed fibres in a decorticate monkey brain crossing the degenerated internal capsule and connecting the nucleus ventralis anterior with the globus pallidus. Because none of these fibres degenerated after pallidal lesions they considered it probable that their direction was from thalamus to globus pallidus. In monkeys Walker (1938*a*) found the nucleus ventralis anterior intact after hemidecortication and this has been confirmed by Mettler (1947).

The mid-line and intralaminar nuclei were unaffected in our case and this is in agreement with the findings of most investigators. Rose and Woolsey (1943, 1949), however, report degeneration of these nuclei in rabbits after removal of "the so-called 'rhinencephalon' and the striatum and amygdala," and in a cat after removal of "the frontal end of the hemisphere as far back as the corpus callosum." They suggest that these nuclei project either upon "rhinencephalic" cortex or subcortical ganglia, or both. Fortuyn (1950), who obtained similar results, concludes that connexions with the striatum are more probable. In these extensive lesions, however, the question arises whether degeneration of the nuclei may not be due to impairment of the vascular supply; the exceptionally dense gliosis at the sites of these nuclei in the photomicrographs illustrating the papers of Rose and Woolsey lends some support to this criticism.

By stimulation of the intralaminar nuclei in cats Morison and Dempsey (1942) produced diffuse recruiting responses in the cerebral cortex, and Jasper (1949) has confirmed this in monkeys as well as in cats. It has been suggested that the cells of the intralaminar nuclei project directly to the cortex. McLardy (1951), however, has brought forward anatomical arguments against such a direct projection and he considers that an intrathalamic diffusion system is more consistent with the available evidence. The complete preservation of the intralaminar nuclei in the present case tends to support McLardy's concept.

It is now accepted that the centre-median nucleus has no cortical projection and the work of C. and O. Vogt (1941), Freeman and Watts (1947) and McLardy (1948) indicates that it is connected with the corpus striatum. The partial cell-loss found in the present case is probably the result of the operative injury and subsequent necrosis of the striatum. The extent of the degeneration in the nucleus, however, does appear to be out of proportion to the damage of the striate body.

The reticular nucleus showed a marked reduction in the number of cells, but those cells that remained were normal in appearance; this is comparable with the findings of Lashley (1941) and Combs (1951) in the rat. This observation suggests that at least some of the cells of the nucleus project directly to the cortex and that the other cells are connected with the ventral and lateral nuclei (Walker, 1938*a*).

The appearance of the cells in the surviving ventral lamina of the

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left lateral geniculate nucleus is also of interest. Though they are very grossly degenerated they are somewhat better preserved than the cells in the two dorsal laminæ. This is difficult to explain, as complete removal of the striate cortex in monkeys has almost invariably caused complete degeneration of the lateral geniculate nucleus on the same side (Polyak, 1932). Even a restricted lesion in the visual cortex results in an area of degeneration in which all the laminæ are equally affected. In monkeys Polyak found that the cells of the lateral geniculate nucleus undergo complete retrograde degeneration within twenty-two days of cortical ablation and, using the same experimental animal, we have seen a sharply localized zone of degeneration in this nucleus with complete disappearance of the cells twenty-four days after a small lesion in the visual cortex. Brouwer (1930) reported a case in which a small lesion in the human visual cortex caused localized degeneration in all laminæ of the lateral geniculate nucleus; he states, however, that the large cells of the ventral laminæ in man are more frequently spared after occipital damage. In one of his hemidecorticate monkeys Walker (1935) described the lateral geniculate nucleus as "degenerated except for a few cells in the lower two layers, though even these cells appear altered." Balado and Franke (1937), contrary to other authorities, concluded that the ventral two laminæ project to the superior corpus quadrigeminum and not to the striate cortex. However, this conclusion appears to be based mainly on one case in which, after destruction of the posterior commissure and superior corpus quadrigeminum by a pineal tumour, they describe partial cell loss, probably bilateral, in these two layers. But they do not describe their method of counting the cells and there is no indication that the small difference in their figures is statistically significant.

Summary

The retrograde cell degeneration in the human thalamus twenty-four days after a practically complete hemidecortication is described. In the ventral nuclei 40–50 per cent of the total number of cells persist up to this time, showing only slight changes in staining properties and in the appearance of the Nissl substance. Details of the morphology and distribution of these residual neurons are given. The dorsomedial nucleus is completely degenerated except for the magnocellular element and small groups of cells connected with the spared cerebral cortex. The mid-line and intralaminar nuclei, as well as the nucleus limitans and parafascicular nucleus, show no evidence of any change. The centre-median and reticular nuclei show partial cell loss. The cells of the ventral, large-celled lamina of the lateral geniculate nucleus are not degenerated to the same degree as those of the small-celled laminæ. The anterior nuclei, pulvinar and medial geniculate nucleus all show complete degeneration. The possible significance of these findings is discussed.

ACKNOWLEDGMENTS

I wish to acknowledge my gratitude to Professor W. E. Le Gros Clark for his supervision and generous advice. My thanks are also due to Mr. E. Thompson who prepared the histological sections and to Mr. F. M. Blackwell who was responsible for the photography.

REFERENCES

BALADO, M., and FRANKE, E. (1937) Das Corpus Geniculatum Externum. Berlin; J. Springer.

BRODAL, A. (1939) *Ztschr. f. d. ges Neurol. u. Psychiat.*, **166**, 646–704.

—— (1940) *Arch. Neurol. & Psychiat.*, **43**, 46–58.

BROUWER, B. (1930) *J. fur Psychol. u. Neurol.*, **40**, 147–159.

COMBS, C. MURPHY (1949) *J. Comp. Neurol.*, **90**, 373–402.

—— (1951) *J. Comp. Neurol.*, **94**, 123–175.

COOK, WILLIAM H., WALKER, JOHN H., and BARR, MURRAY L. (1951) *J. Comp. Neurol.*, **94**, 267–292.

FORTUYN, J. DROOGLEVER (1950) *Folia Psychiat. Neurol. et Neurochirurgica Neerlandica*, **53**, 213–254.

FREEMAN, W., and WATTS, J. W. (1947) *J. Comp. Neurol.*, **86**, 65–93.

GLEES, P., and LE GROS CLARK, W. E. (1941) *J. Anat.*, **75**, 295–308.

JASPER, H. (1949) *E.E.G. & Clin. Neurophysiol.*, **1**, 405–420.

LASHLEY, K. S. (1941) *J. Comp. Neurol.*, **75**, 67–121.

LE GROS CLARK, W. E. (1949) *IV Congres Neurol. Internat.* Paris. Manon et Cie., Editeurs.

——, and RUSSELL, D. S. (1940) *J. Neurol. & Psychiat. (N.S.)*, **3**, 123–140.

MCLARDY, T. (1948) *Brain*, **71**, 290–303.

—— (1950) *J. Neurol. Neurosurg. Psychiat.*, **13**, 198–202.

—— (1951) *E.E.G. & Clin. Neurophysiol.*, **3**, 183–188.

METTLER, F. A. (1947) *J. Comp. Neurol.*, **86**, 95–117.

MEYER, M. (1949) *Brain*, **72**, 265–296.

MORISON, R. S., and DEMPSEY, E. W. (1942) *Amer. J. Physiol.*, **135**, 281–292.

POLYAK, S. (1932) The Main Afferent Fibre Systems of the Cerebral Cortex in Primates. Vol. II, University of California Press.

RANSON, S. W., and RANSON, S. W., Jnr. (1942) *Res. Publ. Ass. Nerv. Ment. Dis.*, Vol. 21. Diseases of the Basal Ganglia.

ROSE, JERZY E., and WOOLSEY, CLINTON N. (1943) *Bull. Johns Hopkins Hospital*, **73**, 65–128.

——, —— (1949) *E.E.G. & Clin. Neurophysiol.*, **1**, 391–404.

SHEPS, JACK G. (1945) *J. Comp. Neurol.*, **83**, 1–56.

VOGT, C., and VOGT, O. (1941) *J. fur Psychol. u. Neurol.*, **50**, 32–154.

WALKER, A. EARL (1935) *J. Comp. Neurol.*, **62**, 407–420.

—— (1938*a*) The Primate Thalamus. University of Chicago Press, Chicago.

—— (1938*b*) *J. Comp. Neurol.*, **69**, 487–507.

WARWICK, R. (1950) *Brain*, **73**, 532–543.

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PLATE VIII

FIG. 1.—Coronal section of the brain just anterior to the thalamus: the spared part of the gyrus rectus on the left side can be seen.

FIG. 3.—Photomicrographs (× 50) of corresponding areas of the mid-line and dorsomedial nuclei of the normal (*a*) and affected sides (*b*) showing the complete preservation of the mid-line nuclei and the total degeneration of the adjacent part of the dorsomedial nucleus in the affected thalamus.

PLATE IX

FIG. 4.—Photomicrographs (× 100) of corresponding areas of the nucleus ventralis lateralis of the normal (*a*) and affected sides (*b*) showing in the latter the proportion of well-preserved residual cells.

FIG. 5.—Photomicrographs (× 100) of corresponding areas of the nucleus ventralis posterior of the normal (*a*) and affected sides (*b*) showing in the latter approximately the same proportion of residual cells as in nucleus ventralis lateralis.

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PLATE VIII

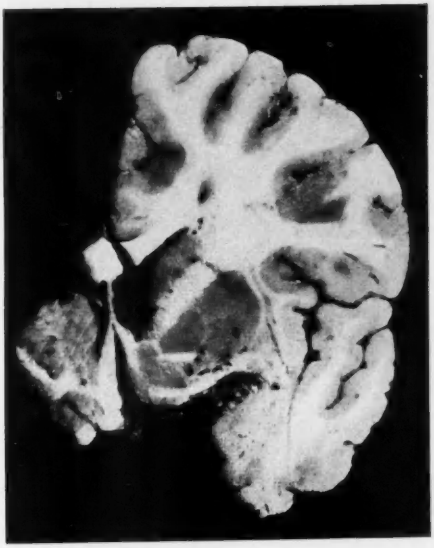
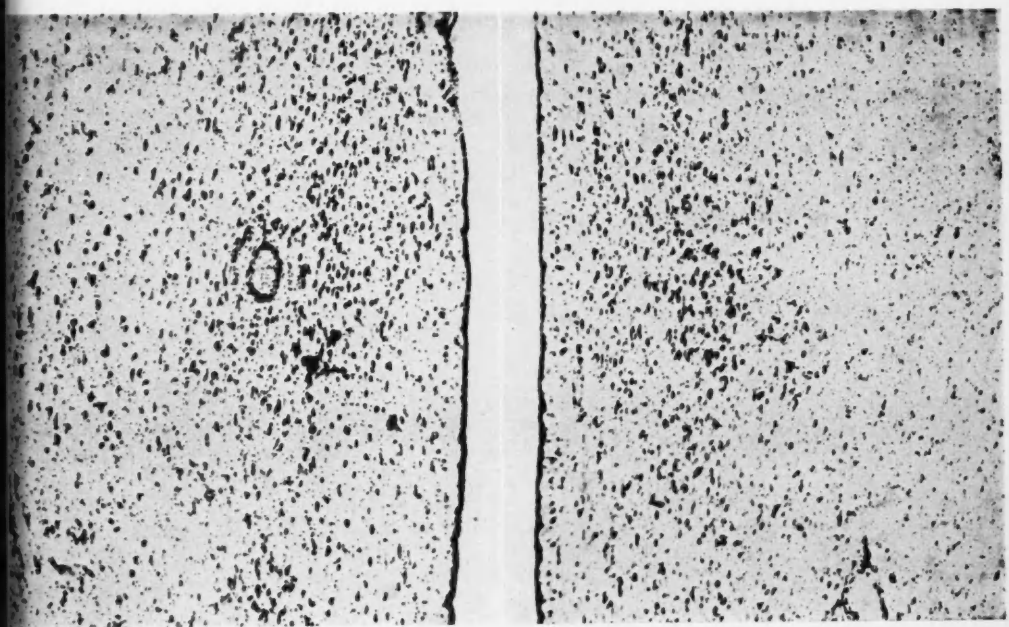


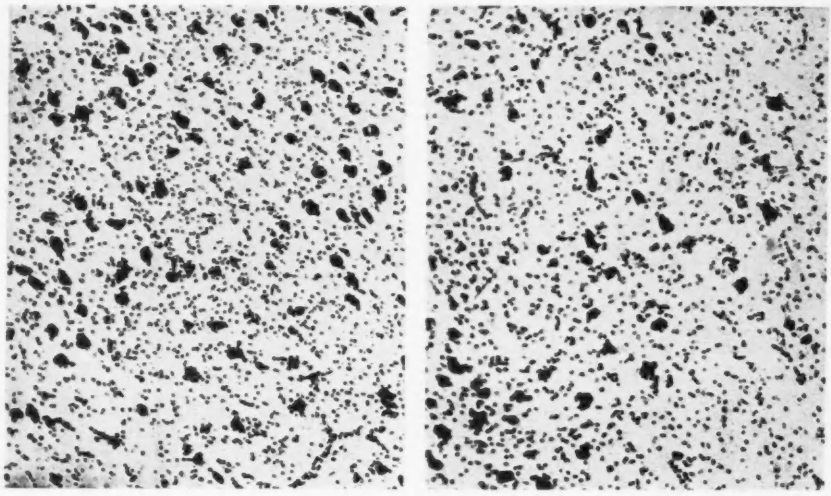
FIG. 1.



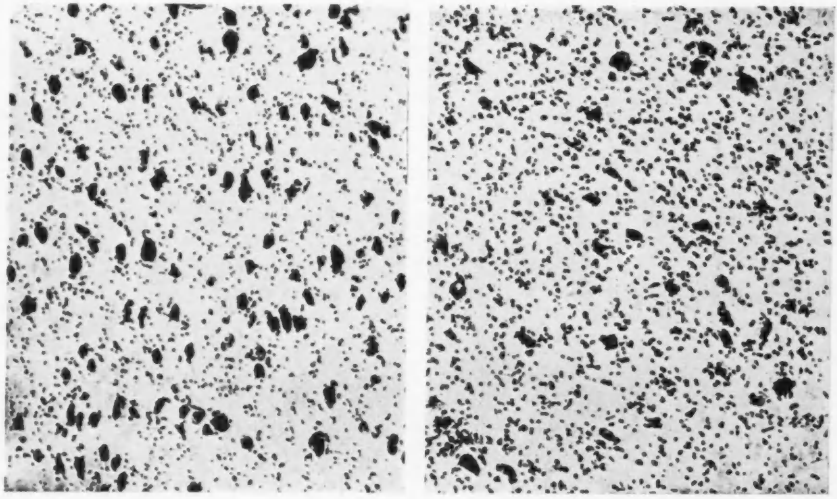
a FIG. 3. *b*

To illustrate article by T. P. S. Powell.

PLATE IX



a FIG. 4. *b*



a FIG. 5. *b*

To illustrate article by T. P. S. Powell.

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DISTURBANCES OF SENSATION OCCURRING IN AN AREA NOT INNERVATED BY THE SEVERED NERVE

BY

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In a series of approximately 350 patients with peripheral nerve injuries investigated by the author there were 3 in whom severance of the ulnar nerve at the wrist was accompanied by impairment of sensation in the area normally supplied by the medial cutaneous nerve of the forearm. A similar finding has been reported by Richards (1945) who observed, preoperatively, "diminished sensation over the inner side of the forearm in some cases of ulnar neuritis." This unusual sensory phenomenon is a striking clinical feature when it occurs and requires an explanation.

Case history.—One case history will suffice to illustrate the nature of the disturbance of cutaneous sensation which was observed external to the territory supplied by the severed nerve.

P. D. lacerated his right wrist on 2.3.51. The ulnar nerve and vessels, and the sublimis and profundus tendons to the ring and middle fingers were severed. These structures were repaired five hours after the injury.

The patient was first examined by the author two months later. At this time there was no recovery in the ulnar field while all modalities of sensation were markedly diminished over the entire field of the medial cutaneous nerve of the forearm. There was no note of this defect in the patient's clinical history but, when questioned, he stated that the feeling down the inner side of the forearm had been "peculiar" since the time of the injury. This proximal sensory defect was a striking feature, particularly in view of the distal site of the injury, and was confirmed by a number of observers. It persisted with little change and was confirmed on 8.6.51, 12.7.51, 9.8.51, 13.9.51, 11.10.51 and 16.11.51. When the patient was last examined on 12.3.52 sensation was still defective over a reduced area involving the medial aspect of the forearm.

In the other 2 patients investigated the examinations were not conducted sufficiently frequently to permit a study of the manner in which normal sensation was restored. However it occurred rapidly and was not accompanied by any signs suggestive of regeneration such as were regularly observed in the field of the repaired ulnar nerve.

Impairment of sensation of the type under review was occasionally observed after severance of the ulnar nerve at more proximal levels, and was also observed in other situations following injury of other nerves.

[1]This work was assisted by a grant from the National Health and Medical Research Council of Australia.

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This material was discarded, however, because the extent of the trauma made it difficult to exclude the possibility that simultaneous damage to adjacent nerve trunks might be a contributing factor. It is interesting that the course of the recovery in some of these cases did not conform to that occurring as the result of regenerating dendrites entering the denervated area.

Cases of severance of the ulnar nerve at the wrist are, however, particularly suitable for studying this phenomenon because in such injuries the medial cutaneous nerve of the forearm escapes involvement or, if it is involved, only the most terminal filaments are injured.

Discussion

Richards (1945) attributed the pre-operative finding of diminished sensation over the inner side of the forearm in some of his cases of ulnar neuritis to pressure on the posterior branch of the nerve where it passed directly over the prominent medial epicondyle of the humerus. Such a factor could not have been responsible in the cases investigated in the present study. In these the ulnar nerve had been severed at the wrist and there was nothing to suggest involvement of the medial cutaneous nerve of the forearm at, or in the vicinity of, a normal elbow. Two possible explanations require consideration.

At the time of the injury terminal filaments of the medial cutaneous nerve of the forearm may also have been severed at the wrist with a resulting retrograde reaction of sufficient severity to impair the function of the affected neurons. In this way the uninjured branch filaments of the severed fibres would be affected and as a result sensation would be impaired in the area innervated by them. Extensive impairment of sensation, such as that involving the entire field of the medial cutaneous nerve of the forearm, could only occur under these conditions, however, if the dendrites branched at proximal levels so that individual neurons innervated larger territories than are customarily attributed to them. That such an arrangement does obtain is suggested by recent work on the branching of nerve fibres in which it has been shown, on the basis of total nerve fibre counts at two levels, that individual fibres branch while coursing in human cutaneous nerve trunks (Lavarack, Sunderland and Ray, 1951). Though the existence of this branching was demonstrated in the upper forearm and leg it probably occurs at various levels between the parent neuron and the periphery. Though details relating to the extent of this branching are not available it is clear that the territory served by a neuron is more extensive than the penultimate branching at the periphery would indicate and that a mechanism is provided whereby widely separated tissues can be brought under the influence of one neuron. Thus the correct picture of the peripheral sensory nervous system is not of single fibres going to well-defined terminations, but of fibres whose complex branching cannot be observed by ordinary histological methods.

For the foregoing explanation to be valid the retrograde changes must be sufficiently severe to affect significantly the function of neurons and their uninjured processes. Damage to only a proportion of the most terminal filaments of the medial cutaneous nerve of the forearm is unlikely to do this, however, because the central neuronal reaction is believed to be minimal after injuries involving the terminal parts of nerve fibres (Buzzard and Greenfield, 1921; Bielschowsky, 1932; Geist, 1933). Moreover, there is the further difficulty that we do not know whether individual fibres *which reach the wrist* spread their branches over the region between the elbow and the wrist.

The anomalous sensory defect could still, however, be accounted for on the basis of fibre branching. Thus it is possible that individual posterior root ganglion cells may furnish fibres to two or more large peripheral nerves (fig. 1). Under such conditions it is not difficult to envisage fibres

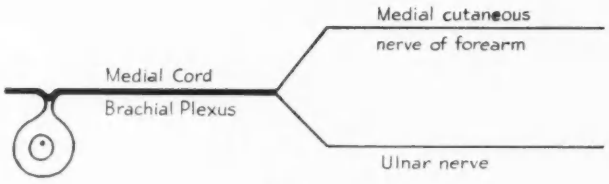

FIG. 1.

running in the medial cord of the brachial plexus which ultimately divide, one branch entering the ulnar nerve and another the medial cutaneous nerve of the forearm. In this way a neuron may serve two widely separated cutaneous areas—one somewhere over the medial aspect of the forearm and another in the cutaneous field of the ulnar nerve. Collectively these neurons could account for the entire area served by the medial cutaneous nerve of the forearm and the ulnar nerve.

Following severance of the entire trunk of the ulnar nerve at the wrist, the retrograde changes are likely to be more severe and more extensive than those occurring after laceration of the terminal filaments of the medial cutaneous nerve of the forearm in the same injury. They are also more likely to be severe enough to cause the entire affected neuronal system to fail as a conducting mechanism. Under these conditions that portion of the neuronal system proceeding distally in the form of an uninjured fibre in the medial cutaneous nerve of the forearm would be affected and this would lead to the appearance of a sensory defect in an area served by a peripheral nerve which had not been damaged. In this way the extensive nature of the sensory defect could be explained.

Thus one explanation involves a pattern in which a neuron supplies two separate areas, possibly circumscribed, over different peripheral nerves while, in contrast, the other depends upon an arrangement in which the

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dendrite of individual neurons distributes filaments, by extensive branching, over the entire medial aspect of the forearm. The weight of evidence favours the former but, whichever arrangement obtains, our uncertainty and the necessity to speculate in these matters does direct attention to the need for more precise information about the branching of nerve fibres.

Retrograde neuronal effects following nerve injury are of variable severity and duration and it may be that in most cases they are not sufficiently severe to lead to an anomalous impairment of sensation which can be detected by clinical testing. On the other hand, if the parent neurons should perish the sensory defect will have some degree of permanency. After such distal injuries, however, the retrograde effects should be minimal and should be followed by an early recovery of the cells and all their surviving processes. Signs of this recovery are reflected at the periphery in two ways. Firstly in the form of regenerating sprouts which emerge from the proximal stump of the severed nerve, in this case the ulnar. Secondly in the form of a rapid restoration of sensation in the cutaneous area supplied by the uninjured branches of the peripheral processes of the affected neurons which are proceeding distally in another peripheral nerve, in this case the medial cutaneous nerve of the forearm.

The extension of such a concept to other nerves and other cutaneous areas may account for many of the unusual sensory phenomena which accompany some nerve injuries and for the tendency for some minor injuries to be followed by widespread effects.

Summary

(1) Disturbances of sensation occurring in an area not innervated by the severed nerve are reported.

(2) An attempt has been made to explain this phenomenon on the basis of the branching of nerve fibres which results in individual neurons innervating larger territories than are customarily attributed to them.

References

Bielschowsky, M. (1932) Histopathology of Nerve Cells. W. Penfield's Cytology and Cellular Pathology of the Nervous System. Hoeber: New York.

Buzzard, E. F., and Greenfield, J. G. (1921) Pathology of the Nervous System. Constable: London.

Geist, F. D. (1933) *Arch. Neurol. Psychiat.*, **29**, 88.

Lavarack, J. O., Sunderland, S., and Ray, L. J. (1951) *J. Comp. Neurol.*, **94**, 293.

Richards, R. L. (1945) *Edinb. med. J.*, **52**, 14.

AN UNUSUAL DISTURBANCE OF MUSCLE FUNCTION RESULTING FROM SEVERANCE OF PERIPHERAL NERVES

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THE object of this paper is to record and discuss an unusual disturbance of muscle function which is occasionally observed after severance of a major peripheral nerve. The significant features of the condition presented in these cases, which in the author's experience have been confined to injuries of the median nerve at the wrist, may be summarized in general terms.

Following clean severance of the median nerve at the wrist, electrical and clinical tests demonstrated paralysis of most or all of the intrinsic muscles of the thumb. The affected muscles remained in this condition for approximately one week when some commenced to contract, feebly at first and then progressively more strongly until finally, two to twelve weeks after the injury, they had either fully recovered or were left with a residual paresis. The significant feature about this recovery was that it was often well advanced before the nerve was repaired, or, if an immediate suture had been performed, long before signs of regeneration were evident in the repaired pathways. Furthermore, blocking the ulnar nerve during the period of this recovery led to the paralysis of all the intrinsic thenar muscles thereby indicating that the early appearance of voluntary contractions observed in the muscles originally paralysed as a result of the injury was due to an ulnar innervation.

This atypical involvement and recovery were observed in muscles which received a double innervation and in others which appeared to be innervated solely by the uninjured ulnar nerve.

The onset of recovery, in muscles paralysed by the severance of a nerve, long before it could be due to the regeneration of axon pathways has been noted by many and is an argument which has been advanced in support of the concept of spontaneous recovery in united nerves without the occurrence of degeneration and regeneration. Such beliefs have become discredited as the result of an increased awareness of the variations in innervation of the thenar muscles together with the introduction of nerve block as a diagnostic procedure. Though it is clear that such early recovery can be accounted for on the basis of an ulnar innervation certain features

[1]This work was assisted by a grant from the National Health and Medical Research Council of Australia.

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relating to the paralysis and recovery remain unexplained. Why are the thenar muscles paralysed by severance of the median nerve if they are innervated by an uninjured ulnar nerve? What is the explanation of the transient nature of the paralysis and why is the progress of the recovery often a slow rather than a sudden process? These are puzzling features which call for comment.

Four possible explanations may account for the anomalous behaviour of muscles after severance of nerves.

(1) It is well known that some or, more rarely, all of the intrinsic thenar muscles may be doubly innervated from median and ulnar sources. Whether this double innervation involves individual fibres or whether the arrangement is one in which a variable number of the muscle fibres is innervated by one nerve and the remainder by the other is not clear. It is known that human muscle fibres will, under certain rather exceptional circumstances, develop a double innervation: there is no evidence that this is the normal arrangement in man (Sunderland, 1952).

Assuming an arrangement in which some muscle fibres are innervated by the ulnar and the remainder by the median nerve it remains to be explained why the ulnar innervated units become quiescent after severance of the median nerve. The slow recovery under such circumstances could, of course, be due to readjustments, either of a central or peripheral nature, which compensate for the denervation of a quota of the muscle fibres. Contributing compensatory mechanisms could be modifications of central patterns of activity, the hypertrophy of surviving muscle fibres, and sprouting from the axons of the uninjured nerve which may extend to innervate the denervated fibres and in this way extend the territory served by the uninjured nerve.

The local reinnervation of denervated muscle fibres by invading axon sprouts which bud from neighbouring intact axons requires further consideration. The development of such ingrowths has been reported in the cat, rat and rabbit by Wehrmacher and Hines (1945), Hines, Wehrmacher and Thomson (1945), van Harreveld (1945), Weiss and Edds (1945), Edds (1949) and Hoffman (1950). Some of these reports also contain references to the quality of the recovery which is attributed to this local reinnervation. Whether or not such intramuscular axon sprouting occurs in man is not known. Even if it is assumed that such a factor does operate it could only modify the clinical picture by extending the territory served by the uninjured nerve. This would assist recovery but obviously fails to explain why the ulnar innervated muscle fibres are rendered inactive by severance of the median nerve. A further difficulty in accepting such an explanation is that the atypical recovery may involve thenar muscles which, so far as can be judged by nerve block and clinical testing, are innervated solely by the ulnar nerve. Under these conditions there are no denervated fibres to stimulate axon sprouting in the muscle rendered temporarily quiescent as a result of the injury.

(2) A more reasonable explanation is provided by recent work on the branching of nerve fibres in which it has been shown, on the basis of total nerve fibre counts at two levels, that individual fibres branch while coursing in human cutaneous nerve trunks (Lavarack, Sunderland and Ray, 1951). Though the existence of this branching was demonstrated in the upper forearm and leg it probably occurs at various levels between the parent neuron and the periphery. Such branching, which has been reported in motor nerves in the cat (Cooper, 1929; Eccles and Sherrington, 1930) is also probably a feature of human motor fibres but this is at present being investigated. Though precise information about the extent of this branching is lacking it is clear that the territory served by a neuron is more extensive than is indicated by the penultimate branching of nerve fibres at the periphery.

Assuming that human motor fibres branch, as do human cutaneous fibres, it is conceivable that the same anterior horn cell may supply fibres to a muscle which reach it over different peripheral nerves (fig. 1).

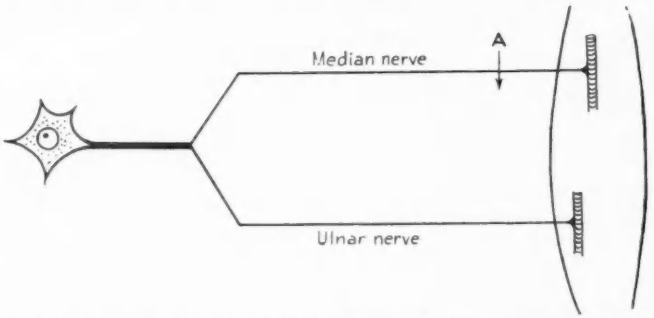

FIG. 1.—Diagrammatic representation of a muscle innervated by a motor neuron which sends fibres to it, by a process of axon branching, over two peripheral nerves. For simplification only one division of the axon is illustrated and each branch is shown innervating only one muscle fibre.

Severance of the median nerve at A leads to retrograde neuronal effects which temporarily abolish conduction in the fibre running in the ulnar nerve. As a result the entire muscle is paralysed. Voluntary activity reappears in the muscle with the recovery of the neuron and the fibre in the ulnar nerve. Recovery of the muscle fibres innervated by the severed nerve is delayed until they are reinnervated by regenerated axons.

Thus it is not difficult to envisage axons of anterior horn cells which innervate the thenar muscles dividing, one branch entering the ulnar nerve and the other the median, and that over these separate pathways the branches are ultimately directed to the same thenar muscle. In this way each neuron may innervate some fibres of a muscle by way of one peripheral nerve and other fibres by another nerve. A further possibility concerns an innervation by the same neuron of muscle fibres in different muscles of the thenar group.

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It is known that section of a peripheral nerve leads to retrograde changes, of variable severity and duration, in some of the parent neurons. Our knowledge of these retrograde changes is based essentially on studies of the reaction occurring in the cell body because the characteristic behaviour of the Nissl material to injury provides such a convenient indicator of intracellular activity. However, it is reasonable to assume that the entire neuronal system central to the site of injury is affected and that, on occasion, the central disturbances may be sufficiently severe to lead to the failure of the entire system as a conducting mechanism.

Returning now to the particular type of injury under review it is conceivable that the injury to the median nerve may be sufficiently severe to precipitate central changes which could affect the uninjured axon branches which are passing to the thenar muscles in the ulnar nerve and in this way block conduction in them. Such an injury would lead to paralysis of the thenar muscles. The median supplied muscle fibres would suffer as the direct result of severance of the median nerve while the ulnar innervated fibres would be affected indirectly because of the retrograde changes in anterior horn cells whose axons have branched to send one process into the median and another into the ulnar nerve.

Retrograde effects are said to be least severe after injuries at the periphery of the limb (Buzzard and Greenfield, 1921; Bielschowsky, 1932; Geist, 1933). If this be so the retrograde effects after injuries of the median nerve at the wrist should be minimal and followed by an early recovery of the cells and all their surviving processes. Signs of this recovery would become apparent at the periphery in two ways. Firstly as regeneration of the axon in the form of sprouting at the site of injury and secondly by the reappearance of voluntary activity in the muscle tissue innervated by the uninjured axon branches of the affected neurons. Thus the thenar muscle fibres innervated via the ulnar nerve would sustain only a temporary paralysis, the duration and severity of which would be influenced by the time taken for the affected neurons to recover and the quality of that recovery. On the other hand, the muscle fibres innervated by the severed axon branches travelling in the median nerve would suffer a more prolonged paralysis which would only be corrected when regenerating axons reached and established functional relationships with them.

(3) A third possibility concerns the temporary failure of central patterns of activity due to trans-synaptic or other disrupting influences. When a muscle is innervated by both the median and the ulnar nerves it is conceivable that its normal activity is determined by the co-ordinated action of groups of motor neurons at central levels which combine to innervate the entire muscle but over separate named peripheral nerves. These patterns of activity may be so delicately adjusted that the exclusion of one or more units as the result of retrograde neuronal changes following severance of axons would almost certainly disorganize the others and in

this way lead to the failure of the entire system. Paralysis of the muscle would follow, some fibres failing because of the severance of their axons and others because of the cessation of activity in the neurons innervating them. The recovery of neurons, together with central adjustments of a compensatory nature, would lead to the reappearance of voluntary contractions in those fibres whose function had been temporarily suspended. On the other hand, the recovery of those fibres originally innervated by the severed axons would be delayed until they were reinnervated by regenerated axons.

(4) It might be argued that, at the time the median nerve was severed, the ulnar nerve had sustained a minor injury which blocked conduction temporarily in its fibres. This is the type of injury which Seddon (1943) has defined as neurapraxia but which elsewhere has been classified as a first degree injury (Sunderland, 1951). Cases in which the median nerve is severed and the ulnar nerve involved in this way undoubtedly occur but, for the following reasons, this possibility was excluded when the cases which form the basis of this report were being investigated. No difficulty was experienced in distinguishing between a first-degree injury of the ulnar nerve and the involvement of some fibres as a result of retrograde neuronal changes secondary to severance of the median nerve. In the former all the muscles in the hand innervated by the ulnar nerve were paralysed. Sensation was usually lost in the classical fashion but sometimes cutaneous sensation was spared, presumably because in a first-degree injury (neurapraxia) the cutaneous fibres are less susceptible to damage than are the remainder. On the other hand, in the cases under discussion in this paper there was no evidence, at the time of the injury, that the ulnar nerve had been damaged. All forms of sensation were normal in the ulnar field. Motor function was also unaffected with the exception of the thenar involvement all of which, bearing in mind variations in innervation, could have been due to severance of the median nerve. Involvement of ulnar fibres innervating thenar muscles was only suspected when signs of an atypical recovery appeared. This was later confirmed by nerve block. If under these conditions one is to persist in the belief that direct injury to the ulnar nerve was responsible then it must be further inferred that only those ulnar fibres innervating the thenar muscles were injured, the others escaping completely. There is, however, no intraneural fibre localization at the wrist which would favour such an interpretation (Sunderland, 1945). It is therefore concluded that recovery from a first-degree injury of the ulnar nerve could not have been responsible for the phenomenon reported in this paper.

The extension of such concepts to other nerves and other situations may account for many of the unusual motor phenomena which accompany some nerve injuries.

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SUMMARY

(1) The appearance of motor recovery in the field of a severed nerve before it could be due to the regeneration of axon pathways is reported.

(2) Four possible explanations which could account for this phenomenon are discussed.

REFERENCES

BIELSCHOWSKY, M. (1932) Histopathology of Nerve Cells in W. Penfield's Cytology and Cellular Pathology of the Nervous System. Hoeber: New York.

BUZZARD, E. F., and GREENFIELD, J. G. (1921) Pathology of the Nervous System. Constable: London.

COOPER, S. (1929) *J. Physiol., Lond.*, **67**, 1.

ECCLES, J. C., and SHERRINGTON, C. S. (1930) *Proc. Roy. Soc., Lond.*, **106**, 326.

EDDS, MACV. (1949) *Anat. Rec.*, **103**, 534.

GEIST, F. D. (1933) *Arch. Neurol. Psychiat.*, **29**, 88.

VAN HARREVELD, A. (1945) *Amer. J. Physiol.*, **144**, 477.

HINES, H. M., WEHRMACHER, W. H., and THOMSON, J. D. (1945) *Amer. J. Physiol.*, **145**, 48.

HOFFMAN, H. (1950) *Aust. J. exp. Biol. med. Sci.*, **28**, 383.

LAVARACK, J. O., SUNDERLAND, S., and RAY, L. J. (1951) *J. Comp. Neurol.*, **94**, 293.

SEDDON, H. J. (1943) *Brain*, **66**, 237.

SUNDERLAND, S. (1945) *Brain*, **68**, 243.

—— (1951) *Brain*, **74**, 491.

—— (1952) The multiple motor innervation of individual muscle fibres in man. In preparation.

WEISS, P., and EDDS, MACV. (1945) *Amer. J. Physiol.*, **145**, 587.

WEHRMACHER, W. H., and HINES, H. M. (1945) *Fed. Proc.*, **4**, 75.

MUSCULAR FASCICULATION AND REACTIVE MYOTONIA IN POLYNEURITIS

BY

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TRANSIENT flickering or vermicular twitching visible in a voluntary muscle, affecting small or larger bundles of muscle fibres without producing any movement of the muscle as a whole, has been designated both muscular "fibrillation" and "fasciculation." The latter term now appears more appropriate not only as indicating that bundles of muscle fibres are involved but also to distinguish the phenomenon from other forms of "fibrillation," such as auricular fibrillation and the fibrillation or fibrillary activity detectable in a denervated muscle on electromyographic exploration.

The cause of fasciculation is not known and even its site of origin is obscure. It was inevitable that a disturbance in the spinal cord should be suspected, as it is in diseases of the anterior horn cells that fasciculation is most frequent. Recent observations, however, have suggested that the site may be peripheral rather than central.

Fasciculation is such a frequent and pronounced feature of motor neurone disease that its occurrence in other disorders is often overlooked or misinterpreted. Polyneuritis, for example, is a condition in which it is sometimes seen, as illustrated by the cases described below.

During the past six years, among several cases of polyneuritis, we have met with seven examples showing the unusual feature of fasciculation in many of the muscles, and in one case, in addition, reactive myotonia was demonstrable in the extensor muscles of both forearms. All the cases were examples of polyneuritis of Guillain-Barré type and had the following features in common:

(1) Early paræsthesia of the extremities, more especially of the hands.

(2) Rapid development of muscular weakness in the limbs.

(3) Subsequent widespread paresis or paralysis of the muscles of the four limbs but especially of the distal portions, that is, the muscles below the elbows and knees including the intrinsic muscles of the hands.

(4) Little or no demonstrable loss of sensation.

(5) No definite tenderness of nerve trunks.

(6) Absent or considerably reduced deep reflexes.

(7) Increase of total protein in the cerebrospinal fluid varying from 60 mg. to 100 mg. per cent.

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(8) Fasciculation in many of the muscles.

(9) Retention of a faradic response in the paresed muscles, and in some instances with only slow relaxation and occasional tetanic spasm on faradic stimulation.

In one of the latter cases, actual reactive myotonia was easily demonstrated in brachioradialis and the extensor muscles of both forearms.

The ages of the 7 patients varied from 14 to 60 years (14, 20, 29, 30, 31, 35 and 60). Before admission to hospital, the presence of fasciculation had led to a provisional diagnosis of motor neurone disease (progressive muscular atrophy) in some of the cases, although admittedly at an unusually early age in 2 of the patients (aged 29 and 31 respectively).

3 of the cases, including the man aged 60, progressed steadily towards full recovery, fasciculation disappearing with return or increase of voluntary movement in the affected muscles. The condition of a girl, aged 20 at the onset, became practically normal after a course of four years; and a boy, aged 14 at the onset, recovered after twenty months except for some persisting weakness in the anterior tibial group of muscles of both legs. One man, aged 29 at the onset, gradually improved over a period of two years and has now remained stationary for three years, showing residual wasting and weakness of the intrinsic muscles of the right hand and of the right forearm. In all these cases fasciculation ultimately disappeared.

The last case, a man aged 31 at the onset of symptoms, was of considerable interest as he showed reactive myotonia in addition to fasciculation. In October 1944 he was serving with the Army in North Africa when he developed weakness of both arms and hands with tingling sensations in all the fingers and both thumbs. These symptoms were followed by weakness in both legs and similar paræsthesia in the feet. According to his hospital card, the cerebrospinal fluid showed a total protein of 90 mg. per cent with normal cells and negative Wassermann and Lange reactions.

When first seen by us in April 1945 almost total paralysis of both arms was present, including pronounced weakness of the deltoids and muscles of the shoulder girdles, and absent arm-jerks excepting that of brachioradialis. Fasciculation was seen in the deltoids, biceps, triceps, muscles of the forearms, and in the intrinsic muscles of both hands. Reactive myotonia but not active myotonia was demonstrated in the extensors of both wrists and in brachioradialis, that on the right side being more pronounced than that on the left. The legs showed considerable loss of power in flexion of the hips and knees. The quadriceps extensor and all muscles below the knee in both lower limbs were very weak but not actually paralysed. The knee and ankle jerks were absent. Faradic responses were present in all muscles; the biceps of the arms tended to develop tetanic spasm on faradic stimulation and the extensors of the wrist were very slow in relaxing. There was no demonstrable sensory loss apart from diminished vibration sense over the tibiæ and at the knees.

The patient gradually improved and on leaving hospital in 1946 he was able to walk fairly well but could rise from a chair only with the aid of his arms. Some degree of voluntary movement was now present in all arm muscles but he could abduct his arms to only just above the horizontal level, and the extensors of the wrist and fingers were still feeble as well as both hand-grips. The knee and ankle jerks remained absent. Fasciculation persisted in the triceps, deltoids and trapezii, and reactive myotonia persisted in the extensors of the wrist.

A year later (May 1947) he had further improved and all muscular actions were performed normally excepting that he was unable to rise from a squatting position without the aid of his arms. Fasciculation had now disappeared from all muscles but reactive myotonia was still present on percussing the right brachioradialis although not the left. The knee and ankle jerks remained absent. Reactive myotonia in the right arm did not disappear until six months later.

Commentary.—Fasciculation was investigated by Denny-Brown and Pennybacker (1938), who supported the theory that the phenomenon was caused by hyperexcitability of the motor neurone, and that it arose within the anterior horn cell. They concluded that the intramuscular twitch represented a contraction of a motor unit, that is, a group of muscle fibres innervated by a single anterior horn cell. Forster and Alpers (1944), however, showed that neither spinal anæsthesia nor peripheral nerve block abolished fasciculation; consequently, they suggested that it must arise in the region of the myoneural junction. Forster, Borbowski and Alpers (1946) further investigated the phenomenon and found that fasciculation persisted for some days after the affected muscle was denervated; they also expressed the view that the twitch was caused by the synchronous contraction of several muscle fibres. Most authors now appear to agree that fasciculation arises in the neighbourhood of the myoneural junction, and at least one group of observers (Masland and Wigton, 1950) have invoked the hypothesis of antidromic impulses as an explanation of spontaneous motor unit activity. Nevertheless, the fact remains that fasciculation is most often seen in the diseases of the spinal cord. It has long been recognized that slow destruction of the anterior horn cells is accompanied by fasciculation, and that in the later stages of such motor neurone disease, when degeneration of motor neurones is presumably complete, fasciculation ceases. Consequently, the conclusion that the anterior horn cells are in some way concerned with the production of fasciculation seems almost inescapable.

The abnormal sensitivity of denervated muscle to drugs, especially acetylcholine (Cannon, 1939), may serve to explain irregular spontaneous twitching in muscle, but it does not explain why in some disorders there occurs spontaneous activity involving only individual muscle fibres, as in the fibrillary activity of denervated muscles detectable by electromyography (fibrillation), while in other diseases a larger amount of muscle

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tissue is involved (fasciculation). As the exact pathological process in motor neurone disease is unknown, it is impossible to determine whether the involuntary muscular activity in this disorder is due to irritation of anterior horn cells by the destroying agent or if it follows partial denervation. Similarly, in syringomyelia, fasciculation may be due either to stimulation of anterior horn cells (or, indeed, internuncial neurones) by the expanding intramedullary cavity, or to actual destruction of the cells. Polyneuritis provides less equivocal evidence because it is an inflammatory process of the peripheral neurones which sometimes affects the anterior cornual cells, and the process is usually reversible. In this disorder, at least, the inference might justifiably be drawn that fasciculation, when it occurs, is secondary to damage to anterior horn cells. The distribution of the irritable muscle fibres, whether the pattern be that of motor unit, anatomical fascicle, or a haphazard group of fibres, is thus determined by the lesion in the spinal cord.

Alajouanine, Lefebvre and Scherrer (1949), in the course of an investigation into muscular cramp, observed the effects of intra-arterial injections of prostigmin. They found that in the normal subject such injections were often followed by fasciculation in "the muscular territory irrigated by the artery," while in patients suffering from disease of the spinal cord or spinal nerve roots the injection, in some cases, transformed fasciculation into muscular cramp. Brown (1937) had already shown that the intra-arterial injection of acetylcholine, when given close to the muscle under investigation, could cause a muscular contraction which clinically appeared to be more sluggish than that following nerve stimulation, and on electromyographic examination consisted of a group of fibrillation potentials, indicating that while acetylcholine could cause muscle to contract, it did not cause the brisk contraction which follows nerve stimulation.

Reactive myotonia during the course of polyneuritis is most unusual. In the case we have described, as the myotonia improved and ultimately disappeared *pari passu* with the other symptoms, it can only be regarded as a symptom of the polyneuritis. It differs, therefore, from the form of myotonia originally described by Talma, in 1892, termed myotonia acquisita, which develops acutely *after* an infection or intoxication. In some of the cases recorded, especially by Krabbe (1921 and 1934), the symptoms of the illness preceding the myotonia have resembled polyneuritis; in other cases the infection or intoxication has been pulmonary tuberculosis, septic lesions or septicæmia, dysentery, typhoid fever, alcoholism or lead poisoning, while in several cases no ætiological factor was apparent. Polyneuritis in most instances either recovers completely or leaves residual muscular atrophy. In some cases, however, recovery appears excessive and the muscles hypertrophy. These hypertrophied muscles, as Krabbe (1934) has pointed out, are very liable to show myotonia.

Myotonia may be an occasional symptom of other lower motor neurone

diseases. For instance, one of us (C. W-D.) demonstrated an example of both active and reactive myotonia in one member of a family group suffering from peroneal muscular dystrophy (Charcot-Marie-Tooth type); the myotonia disappeared after about three years.

The reactive myotonia which was found in the case of polyneuritis described might be attributable to hypersensitivity of muscle fibres following partial denervation. When a needle-electrode is inserted into an affected muscle in a case of dystrophia myotonica, a series of high-frequency discharges is observed, which on analysis is found to consist of a succession of potentials of short duration: this possibly means that muscle tissue in this disorder, being abnormally sensitive to stimulation, undergoes local contraction, the mechanical stimulus of which is sufficient to provoke contraction in the neighbouring muscle tissue. This abnormal sensitivity appears to explain the myotonia in dystrophia myotonica, and it may well be that this is also the explanation in polyneuritis, in which partial denervation sets up a state of hypersensitivity sufficient to cause both fasciculation and myotonia.

Summary

(1) Fasciculation is defined and is distinguished from other forms of muscular fibrillation.

(2) The occurrence of fasciculation in 7 cases of polyneuritis is described.

(3) In addition to fasciculation, the 7 cases all showed early paræsthesia of the extremities, widespread paralysis of the limb muscles, loss of tendon reflexes, little or no demonstrable loss of sensation, increase of total protein in the cerebrospinal fluid and retention of faradic responses in the affected muscles.

(4) In one case, reactive myotonia was present in the extensor muscles and brachioradialis of each forearm.

(5) The various hypotheses as to the nature and site of origin of fasciculation are discussed. The view is advanced that while a disturbance at the myoneural junction may be the immediate exciting cause of the muscle fibre twitch, disease of the spinal cord, and especially of the anterior cornual cells, plays an important part.

(6) It is probable that in those cases of polyneuritis showing fasciculation, the disease-process has spread to the anterior cornual cells.

(7) Reactive myotonia is an occasional but unusual symptom of polyneuritis and other diseases of the lower motor neurone, and is probably due to an abnormal sensitivity of muscle fibres following partial denervation.

REFERENCES

Alajouanine, T., Lefebvre, J., and Scherrer, J. (1949) Essai de l'etude physiopathogenique des crampes musculaires, *Rev. Neurol.*, **81**, 633.

Brown, G. L. (1937) Action potentials of normal mammalian muscle; effects of acetylcholine and eserine, *Journ. of Physiol.*, **89**, 220.

XUM

BROWN, G. L. (1937) The actions of acetylcholine on denervated mammalian and frog's muscle, *Journ. of Physiol.*, **89**, 438.

CANNON, W. (1939) A law of denervation, *American Journ. Med. Sciences*, **198**, 737.

DENNY-BROWN, D., and PENNYBACKER, J. (1938) Fibrillation and fasciculation in voluntary muscle, *Brain*, **61**, 311.

FORSTER, F., and ALPERS, B. (1944) The site of origin of fasciculations in voluntary muscle, *Archives of Neurol. and Psychiat.*, **51**, 276.

——, BORBOWSKI, W., and ALPERS, B. (1946) The effects of denervation on fasciculations in human muscle, *Archives of Neurol. and Psychiat.*, **56**, 276.

KRABBE, K. H. (1921) Les hypertrophies musculaires postnevrites, *Rev. Neurol.*, **37**, 802.

—— (1934) The myotonia acquisita in relation to the post-neuritic hypertrophies, *Brain*, **57**, 184.

MASLAND, R. L., and WIGTON, R. S. (1950) Nerve activity accompanying fasciculation produced by prostigmin, *Journ. of Neurophysiol.*, **3**, 269.

TALMA, S. (1892) Dystrophia muscularis hyperplastica, *Deutsch. Zeitschr. f. Nervenheilk.*, **2**, 197.

WORSTER-DROUGHT, C. (1932) An unusual form of myopathy in a mother and two children, *Proc. Roy. Soc. Med.* (Section of Neurol.), **25**, 60.

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FOR

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